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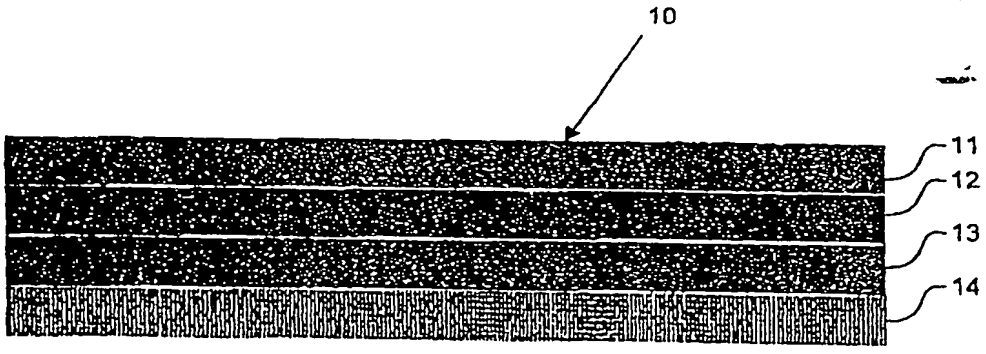

(57) Abstract

A transdermal patch for administering a volatile liquid drug, such as nicotine, transdermally to a patient comprising a four-layer laminated composite of: a top drug impermeable backing layer; a pressure sensitive silicone adhesive layer containing the drug; a pressure sensitive acrylic adhesive layer also containing the drug; and a removable siliconized release liner layer. Also disclosed is a method for treating a person for nicotine dependence and particularly for treating a woman for nicotine dependence.

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TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS

TECHNICAL FIELD

This invention is in the field of transdermal drug delivery devices. More particularly, it relates to a method for making transdermal patches that deliver volatile liquid drugs, such as nicotine, mecamylamine and selegiline, and to the resulting patches. The invention also relates to a method for treating a person for nicotine dependence comprising transdermally administering an effective amount of mecamylamine to the person without transdermal coadministration of nicotine. The invention further relates to a method for treating women for nicotine dependence comprising transdermally co-administering effective doses of mecamylamine and nicotine.

BACKGROUND ART

There are two basic types of transdermal patches that are used to deliver liquid drugs. One is a liquid reservoir patch in which the liquid drug, either neat or dissolved in a carrier, is confined in a pouch or sac within the device. An example of such a device for delivering nicotine is shown in Fig. 1 of U.S. Pat. No. 5,364,630. The other is a matrix patch in which the liquid drug is dissolved in one or more polymeric layers of a laminated composite. Examples of matrix patches that deliver nicotine are described in U.S. Pat. No. 5,603,947. The present invention relates to a matrix patch.

In the manufacture of matrix patches for administering volatile liquid drugs such as nicotine it is common to attempt to avoid steps involving heat treatment, e.g., drying, so as to avoid excessive loss or degradation of the drug. For instance U.S. Pat. No. 4,915,950 and 5,603,947 describe a printing procedure whereby neat nicotine is applied to a nonwoven fabric laminated to a polyisobutylene adhesive layer. Alternatively "hot" melt adhesives that melt at relatively low temperatures have been used as a matrix material for these drugs. See U.S. Pat. No. 5,411,739.

PCT Pub. No. WO 96/40085 describes transdermal matrix patches for administering drugs such as selegiline, nitroglycerin and nicotine, that are liquid at normal room temperature. The publication suggests making a monolithic matrix of the drug in an adhesive by mixing one

or more polymeric adhesives, preferably polyacrylate and polysiloxane, and the drug in a volatile solvent, casting the mixture, and evaporating the solvent. The publication lists as examples of volatile solvents isopropanol, ethanol, xylene, toluene, hexane, cyclohexane, heptane, ethyl acetate and butyl acetate.

When silicone adhesives have been used as the matrix material in nicotine patches the matrix layer has been cast from a heptane solution. See, for instance, Example 1 of U.S. Pat. No. 5,603,947. Other co-solvents, including hexane, have been suggested for use with silicone adhesives used in transdermal devices. See p. 3, line 51, et seq. of EPO 524776 A1.

Mecamylamine is an antagonist to nicotine. U.S. Patent Nos. 5,316,759, 5,726,190, and 5,574,052 teach the coadministration of mecamylamine and nicotine to treat nicotine dependency. These patents do not teach or suggest the transdermal administration of mecamylamine itself to treat nicotine dependency. Furthermore, the prior art does not teach that coadministration of mecamylamine and nicotine is especially effective as a smoking cessation aid specifically suited for women.

DISCLOSURE OF THE INVENTION

One aspect of this invention is a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) a top backing layer that is impermeable to the drug;

b) silicone adhesive layer containing the drug and underlying the backing layer;

c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and

d) a removable release liner layer underlying the acrylic adhesive layer, wherein the combined amount of drug in the silicone adhesive layer and the acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.

Another aspect of the invention is a method of making a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;

b) evaporating the hexane from the coating to form a silicone adhesive layer containing the drug; and

c) laminating a polyacrylate adhesive layer affixed to a release liner layer onto the silicone adhesive layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.

Another aspect of the invention is a method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal coadministration (or other coadministration except by smoking) of nicotine to the person.

A further aspect of the invention is a method for treating a woman for nicotine dependence comprising transdermally coadministering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a elevational cross-sectional view of an embodiment of the invention patch.

Figures 2-6 are graphs of the results of the *in vitro* skin flux tests described in the examples.

Figures 7 and 8 are graphs of the results of the clinical studies described in the examples.

MODES FOR CARRYING OUT THE INVENTION

As used herein the term "volatile liquid drug" intends a drug that (i) is capable of permeating through unbroken human skin at therapeutically effective rates from a patch of practical size, the permeation either being unenhanced or enhanced through coadministration of one or more skin permeation enhancing agents, (ii) is a liquid at 25°C, atmospheric pressure, and (iii) has a boiling point less than about 300°C at atmospheric pressure. Examples of such drugs are nicotine, mecamylamine, selegiline, and nitroglycerine.

As used herein the term "diffusional contact" intends a relationship, either through direct contact or through indirect contact via an intermediary material. between two surfaces or layers such that drug is able to pass by diffusion from one surface or layer to the other surface or layer.

As used herein the term "treating a person for nicotine dependence" intends causing the person to reduce or eliminate his or her intake of nicotine from smoking and/or chewing tobacco on a temporary or permanent basis.

The embodiment of the invention shown in Figure 1 is a four-layer laminated composite matrix type transdermal patch, generally designated 10. The four layers are: (1) a top drug-impermeable backing layer 11; (2) an intermediate drug-containing silicone adhesive layer 12; (3) a basal drug-containing polyacrylic adhesive layer 13; and (4) a removable release liner layer 14.

Materials for making backing layer 11 are well known in the art. They include various polymers such as polyethylene terephthalate, polyethylene, polypropylene and polyvinyl chloride, metal foils such as aluminum foil, and polymer-metal composites.

Adhesive layer 12 is made from a pressure sensitive silicone adhesive. An amine compatible silicone adhesive is preferred for use with drugs, such as nicotine, which contain amine groups. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989). See also Pfister, W.R., et al. "Silicon Adhesives for Transdermal Drug Delivery" Chemistry in Britain (Jan. 1991), pp. 43-46 and EP Pub. No. 0524776 A1. Suitable commercially available silicone pressure sensitive adhesives are available from Dow Corning under the trademark BIO-PSA. The silicone pressure sensitive adhesives are supplied commercially as solutions in a solvent. Per the present invention the solvent should be hexane. The thickness of layer 12 will usually be in the range of about 25 to 100 microns, more usually 50 to 75 microns. Expressed alternatively, the layer 12 will be present at about 4 to 18 mg/cm^2, more usually 8 to 14 mg/cm^2. Adhesive layer 12 initially (before it is laminated to adhesive layer 13) contains the entire drug loading. In this regard, the drug(s) will usually be added to the silicone adhesive in amounts ranging between about 5% to 50% by weight, more usually 10% to 30% by weight, based on the total dry weight of drug and adhesive.

Adhesive layer 13 is made from one or more solution acrylic pressure sensitive adhesives. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 396-456 (D. Satas, ed.) Van Nostrand Reinhold, New

York (1989). They are usually copolymers composed of: 50% to 90% of a main acrylate or methacrylate monomer, usually 2-ethylhexyl acrylate, butylacrylate, or iso-octyl acrylate; 10% to 40% of a modifying monomer such as vinyl acetate; and 2% to 20% of a functional group-containing monomer such as acrylic acid. Examples of suitable commercially available solution acrylic pressure sensitive adhesives are: National Starch DuroTak® adhesives 87-2194 and 87-2070. The thickness of the acrylic adhesive layer 13 will usually be about the same as that of layer 12. After lamination to the silicone adhesive layer 12 and equilibration of the drug between layers 12 and 13, layer 13 will also contain drug. In this regard the drug will usually constitute about 2.5% to 30% by weight, preferably 5% to 15% by weight, of layer 13 after equilibration occurs.

The release liner layer 14 is removed before device 10 is placed on the skin. After layer 14 is removed the lower surface of layer 13 is exposed and defines the basal surface of the device which is intended to be placed directly in contact with the skin. Release liner layers are well known in the transdermal patch art. They are made of materials that permit the layer to be easily stripped or peeled away from the adjacent pressure sensitive adhesive layer. Release liner layers are typically made from drug impermeable polymers such as polyesters which are coated with materials such as silicone or fluorinated hydrocarbons that reduce the adhesiveness between it and the adjacent pressure sensitive adhesive layer. In this regard since the acrylic pressure sensitive adhesive layer rather than the silicone pressure sensitive adhesive layer defines the basal surface of the device it is possible to use a siliconized release liner. Such liners are generally not compatible with silicone adhesives. Siliconized liners are more economical than fluorocarbon coated liners. Further, use of the acrylic pressure sensitive adhesive as the basal layer provides a more controlled and predetermined delivery of the drug than could be achieved using a silicone adhesive basal layer. The particular drug release profile from the patch can be varied by altering the thickness and/or composition of the acrylic pressure sensitive adhesive layer and/or the drug loading, and/or by employing a permeation enhancer.

The drug is released from the surface of the acrylic pressure sensitive adhesive to the skin at a therapeutically effective rate. That rate will depend upon the particular drug. In the case of nicotine, the rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr. In the case of co-administration of nicotine and the mecamylamine, the nicotine rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr, and the mecamylamine rate will usually be in the range of 0.02 to 1 mg/hr, preferably 0.1 to 0.6 mg/hr. In the case of

mecamylamine alone, the rate will usually be in the range of 0.02 to 1 mg/hr. preferably 0.1 to 0.6 mg/hr. In the case of selegiline, the rate will usually be in the range of 0.2 to 3 mg/day. The flux (rate per unit area) of drug from the basal surface of the acrylic pressure sensitive adhesive and the area of that surface are matched to provide the desired rate of drug administration. As indicated, the flux may be varied by altering the drug loading, composition and/or thickness of the acrylic pressure sensitive adhesive layer, and/or by the use of permeation enhancers. The surface area of the layer in diffusional contact with the skin will usually be in the range of 5 to 100 cm^2, more usually in the range of about 10 to 50 cm^2. Each patch may be applied to the skin for periods of from several hours up to about a week, and more preferably for about 1 to 3 days.

The patches of the invention are made in the following manner. The drug(s) is dissolved in the desired proportion(s) in a hexane solution of the pressure sensitive silicone adhesive. The drug(s) will normally constitute about 2.5% to 25% by weight of the solution. This solution is then cast onto the backing layer and allowed to dry. By casting the drug and silicone adhesive from a hexane solution, very low casting and drying temperatures (30°C to 40°C) may be used, thus reducing degradation or loss of the liquid drug(s) during the casting and drying process. Even though low processing temperatures in the 30°C to 40°C range are used, low residual hexane levels (e.g., < 0.1 % by wt.) are found in the layer after about 1 to 5 min. of drying. Other solvents, such as heptane and toluene, are not suitable since they require higher processing temperatures and thus result in more drug degradation and/or evaporation during coating and drying. Other pressure sensitive adhesives such as acrylics or polyisobutylenes are similarly not suitable for formulating liquid drugs since they require higher processing temperatures to remove their solvents (e.g., ethyl acetate, heptane, etc.). The silicone adhesive also has excellent adhesion to the backing. A solution of the acrylic pressure sensitive adhesive is cast onto a siliconized release liner layer and permitted to dry. The acrylic pressure sensitive adhesive/release liner subassembly is then laminated to the drug-containing silicone pressure sensitive adhesive/backing subassembly to form the final laminated composite. After lamination the drug(s) equilibrates in the adjacent adhesive layers. Patches are cut/punched from the composite and placed in appropriate packaging.

Alternatively, the drug and silicone adhesive solution can be cast onto a disposable liner and dried as described. The sub-assembly can be laminated to the acrylic pressure sensitive adhesive/release liner subassembly. The disposable liner is then removed to expose the top surface of the silicone adhesive layer. A backing is then laminated to the top surface of the

silicone adhesive layer to form the final laminated composite. In still another alternative manufacturing scheme, the solution of silicone adhesive and drug is cast directly into the acrylic pressure sensitive adhesive release liner subassembly and dried. A backing is then applied to form the completed laminated composite.

It has surprisingly been found that, in the treatment of nicotine dependence, women respond more favorably to a patch that combines nicotine and mecamylamine than to a patch that contains either nicotine or mecamylamine alone. The patch can be administered while the woman continues to smoke and then ceases smoking or if she chooses to stop smoking at the same time as beginning treatment.

For treatment of nicotine dependence, the patches of the invention are typically worn for a total period of about 3 to 16 weeks. During the first 1 to 4 weeks, preferably 2 to 3 weeks, the patent is allowed to smoke as desired. During the remainder of the treatment, i.e., two to 12 weeks, preferably 4 to 8 weeks, the patient is advised to not smoke.

EXAMPLES

The following examples further illustrate the patches of the invention and the process used to make them. These examples are not intended to limit the invention in any manner.

Example 1: Preparation and Testing of Nicotine Patch

Nicotine was added to a hexane solution of Dow Corning BIO-PSA amine-compatible silicone pressure sensitive adhesive to a level of approximately 12% by weight based on the combined dry weight of adhesive and nicotine. The resulting hexane solution of adhesive and nicotine was coated onto a 3M Scotchpak 1109 polyester/polyolefin backing at 13.8 mg/cm^2 (1.63 mg/cm^2 nicotine and 12.17 mg/cm^2 adhesive) and the coated backing was dried at 30°C to 40°C for about 3 min.

National Starch DuroTak 87 2194 acrylic solution pressure sensitive adhesive was coated onto a 125 micron thick Daubert Coater Products 1-5 PESTR (Matte) - 164Z siliconized polyester release liner at 13.18 mg/cm^2 and the coated release liner was dried at 100°C for about 10 min.

The dried silicone adhesive/nicotine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the nicotine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of nicotine within the layers was about 6% (w/w) after equilibration.

In vitro nicotine flux from the laminated composite was determined at 32°C through human cadaver epidermis into an infinite sink using modified Franz glass diffusion cells. Nicotine assays were made by HPLC.

For comparison purposes the flux of nicotine from commercial Habitrol3 21 mg/day patches was determined using the same test procedure. Figure 2 is a graph of the nicotine flux from the composite of the example and from the Habitrol3 patches versus time.

Example 2: Preparation and Testing of Nicotine/Mecamylamine Patches

Nicotine and mecamylamine were added to a hexane solution of Dow Corning BIO-PSA amine compatible silicone pressure sensitive adhesive. Two batches were made: one contained approximately 10% nicotine and 6.4% mecamylamine based on the total dry weight of the adhesive and the two drugs; and a second contained approximately 10% nicotine and 4.2% mecamylamine, based on the total dry weight of the adhesive and the two drugs. The batches were separately coated onto a 3M Scotchpak 1109 polyester/polyoefin backing film at 9.6 mg/cm^2 (0.96 mg/cm^2 nicotine, 0.61 mg/cm^2 mecamylamine, 8.03 mg/cm^2 adhesive for the first batch; 0.96 mg/cm^2 nicotine, 0.40 mg/cm^2 mecamylamine, 8.24 mg/cm^2 adhesive for the second batch) and then dried at 30 to 40°C for about 2 min.

A blend of two National Starch DuroTak acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w, respectively, was made. The blend was coated at 8.0 mg/cm^2 onto a 75 micron thick Daubert Coater Products siliconized polyester release liner (1-3 PESTR (Matte) - 164Z) and dried at about 100°C for about 10 min.

The drug-containing silicone adhesive/backing subassembly was then laminated to the acrylic adhesive/release liner subassembly to form a four layer/laminated composite. After lamination the nicotine and mecamylamine distributed themselves uniformly within the adjacent

adhesive layers. The concentration of the drugs in the adhesive layers after equilibration was: nicotine, 5.45% (w/w) and mecamylamine 3.47% (w/w) for the composite made from the first batch and 5.45% (w/w) and 2.27% (w/w), respectively, for the composite made from the second batch. Patches about 23 cm^2 in area were cut from the composites. These patches were designed to deliver 21 mg of nicotine and 6 mg of mecamylamine in 24 hr and 21 mg of nicotine and 3 mg of mecamylamine in 24 hr, respectively.

Nicotine and mecamylamine fluxes from the patches were determined using the procedure described Example 1. Mecamylamine assays were made by GC. Figure 3 is a graph showing the nicotine flux from the patches versus time. Patches made from the first batch composite are designated 21/6; those from the second batch composite are designated 21/3. Figure 4 similarly is a graph showing the mecamylamine flux from the patches.

Example 3 Preparation and Testing of Selegiline Patch

Selegiline was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 10% by weight based on the combined dry weight of adhesive and selegiline. The resulting hexane solution of adhesive and selegiline was coated on 3M Scotchpak 1109 polyester/polyolefin backing at 10.0 mg/cm^2 (1.0 mg/cm^2 selegiline and 9.0 mg/cm^2 adhesive) and the coated backing was dried at 30°C to 40°C for about 3 minutes.

National Starch DuroTak® 87-2194 acrylic solution pressure sensitive adhesive was coated onto a 125 micron thick Daubert Coated Products 1-5 PESTER (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm^2 and the coated release liner was dried at about 100°C for about 10 minutes.

The dried silicone adhesive/selegiline-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the selegiline distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of selegiline within the layers in about 5.5% (w/w) after equilibration.

Selegiline flux from the patches was determined using the procedure described in Example 1. Selegiline assays were made by HPLC.

Figure 5 is a graph of the selegiline flux from the composite of this example versus time.

Example 4. Preparation and Testing of Mecamylamine Patch

Mecamylamine was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 6.3% by weight based on the combined dry weight of adhesive and mecamylamine. The resulting hexane solution of adhesive and mecamylamine was coated on 3M Scotchpack 1109 polyester/polyolefin backing at 9.6 mg/cm^2 (0.61 mg/cm^2 mecamylamine and 8.99 mg/cm^2 adhesive) and the coating backed was dried at 30°C to 40°C for about 3 minutes.

A blend of two National Starch DuroTak® acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w. respectively, was made. The blend was coated onto a 75 micron thick Daubert Coated Products 1-2 PESTR (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm^2 and the coated release liner was dried at about 100°C for about 10 minutes.

The dried silicone adhesive/mecamylamine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the mecamylamine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of mecamylamine within the layers is about 3.47% (w/w) after equilibration. Patches about 23 cm^2 in area were cut from the composites. These patches were designed to deliver 6 mg of mecamylamine in 24 hr.

Mecamylamine flux from the patches was determined using the procedure described in Example 1. The mecamylamine assay was done by gas chromotography. Figure 6 is a graph of the mecamylamine flux from the composite of this example versus time; mecamylamine flux through the same section of cadaver skin from the 21/3 and 21/6 compositions of Example 2 are shown for comparison.

Study A.

Patches made according to Examples 1, 2 and 4 and a placebo patch were subject to a clinical study. The study was a multi-center, double-blind, randomized parallel group study. Patients were randomized to receive one of five treatments: nicotine/mecamylamine 21/6; nicotine/mecamylamine 21/3; nicotine (21 mg/24 hr); mecamylamine (6 mg/24 hr) and placebo. Patches were applied daily for the first six weeks of the study. Patients were instructed to continue smoking for the first two weeks and to stop smoking thereafter.

Among the efficacy parameters monitored during the study were four week continuous abstinence after the quit smoking date, nicotine plasma concentration, and ad hoc smoking during the treatment period.

Table 1 below provides the overall abstinence data for the study. In the table "N" represents the number of patients, "No" indicates non-abstinence and "Yes" indicates abstinence. As indicated the nicotine/mecamylamine 21/6 gave the highest abstinence.

Table 1

	Overall	21/6	21/3	21/0	0/6	Pla
N	705	142	141	141	140	141
No	82%	74%	79%	79%	82%	92%
Yes	18%	26%	21%	21%	18%	8%

Figure 7 is a graph showing the mean nicotine plasma concentrations in ng/ml of the patients by treatment and time. As shown, the mecamylamine only patch (0/6) produced a steady decline in nicotine levels even during the initial two-week period of the study. Fig. 8 is a graph showing the mean observed change in the number of cigarettes smoked by treatment and day. Surprisingly, the number of cigarettes smoked did not increase with the mecamylamine only (0/6) treatment, as the literature reports that oral mecamylamine administration increased ad hoc cigarette consumption.

Study B.

A second multi-center, double-blind, randomized parallel group clinical study was conducted. Patients were randomized to receive one of three treatments: nicotine/mecamylamine 21/6; nicotine/mecamylamine 21/3, and nicotine (21 mg/24 hr). Patient instructions were the same as in the first study.

The abstinence data for this study are summarized in Table 2. In this study the nicotine/mecamylamine combination was again more effective than nicotine alone.

Table 2

Treatment	21/6	21/3	21/0
N	180	180	180
Abstinence	29%	29%	23%

A detailed examination of the data the clinical studies yielded a surprising difference in abstinence rates for females and males. In both studies, the abstinence rate for females in the 21/6 treatment group was 31% compared to the 21/0 treatment group rates of 17% in the first study and 18% in the second study. These gender specific data are summarized in Table 3.

Table 3

Study	Gender		21/6	21/3	21/0	0.6	Plac
First	Female	N	70	67	63	75	74
		% Abst.	31	16	17	17	9
	Male	N	72	74	78	65	67
		% Abst.	21	26	24	18	6
Second	Female	N	93	96	91		
		% Abst.	31	29	18		
	Male	N	87	84	89		
		% Abst.	28	29	28		

N = number of subjects in study.

% Abst.= Four-week continuous abstinence results.

Modifications of the above described modes for carrying out the invention that are obvious to persons of skill in the transdermal patch art are intended to be within the scope of the following claims. All publications, patent applications and patents noted above are hereby incorporated by reference.

CLAIMS

1. A transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) a top backing layer that is impermeable to the drug;

b) an intermediate silicone adhesive layer containing the drug and underlying the backing layer;

c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and

d) a removable release liner layer underlying the acrylic adhesive layer,

wherein the combined amount of drug in the silicone adhesive layer and acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.

2. The transdermal patch of claim 1, wherein the drug is nicotine and the patch is capable of administering 0.2 to 1.5 mg nicotine per hour to the patient.

3. The transdermal patch of claim 1, wherein the drug is a combination of nicotine and mecamylamine and the patch is capable of administering 0.2 to 1.5 mg nicotine per hour and 0.02 to 1 mg mecamylamine per hour to the patient.

4. The transdermal patch of claim 1 wherein the drug is selegiline and the patch is capable of administering 0.2 to 3 mg selegiline per day to the patient.

5. The patch of claim 1 wherein the drug is mecamylamine only and the patch is capable of administering 0.02 to 1 mg mecamylamine per hour to the patient.

6. The patch of claim 1 wherein the release liner layer is a siliconized release liner layer.

7. The patch of claim 1 wherein the acrylic adhesive layer is made from a blend of two acrylic adhesives.

8. A method of making a transdermal patch for administering a volatile liquid drug to a patient comprising:

a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;

b) evaporating the hexane from the coating to form a layer of drug-containing silicone adhesive on the backing layer; and

c) laminating an assembly comprising an acrylic adhesive coated onto a release liner layer onto the silicone adhesive layer on the backing layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.

9. The method of claim 8 wherein step b) is carried out at 30°C to 40°C.

10. The method of claim 8 wherein the release liner layer is a siliconized release liner layer.

11. The method of claim 8 wherein the drug is nicotine.

12. The method of claim 8 wherein the drug is a combination of nicotine and mecamylamine.

13. The method of claim 8 wherein the drug is selegiline.

14. The method of claim 8 wherein the drug is mecamylamine only.

15. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal co-administration of nicotine to the person.

16. The method of claim 15 wherein the rate of mecamylamine administration is 0.02 to 1 mg/hr.

17. The method of claim 15 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr.

18. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine to the person for a first time period during which the person smokes cigarettes as desired and continuing said administration for a second time period during which the person is advised to not smoke.

19. The method of claim 18 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.

20. The method of claim 18 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.

21. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman.

22. The method of claim 21 wherein the rate of mecamylamine administration is 0.02 to 1 mg/hr and the rate of nicotine administration is 0.2 to 1.5 mg/hr.

23. The method of claim 21 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr and the rate of nicotine administration is 0.3 to 0.9 mg/hr.

24. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman for a first time period during which the woman smokes cigarettes as desired and continuing said administration for a second time period during which the woman is advised to not smoke.

25. The method of claim 24 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.

26. The method of claim 24 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.

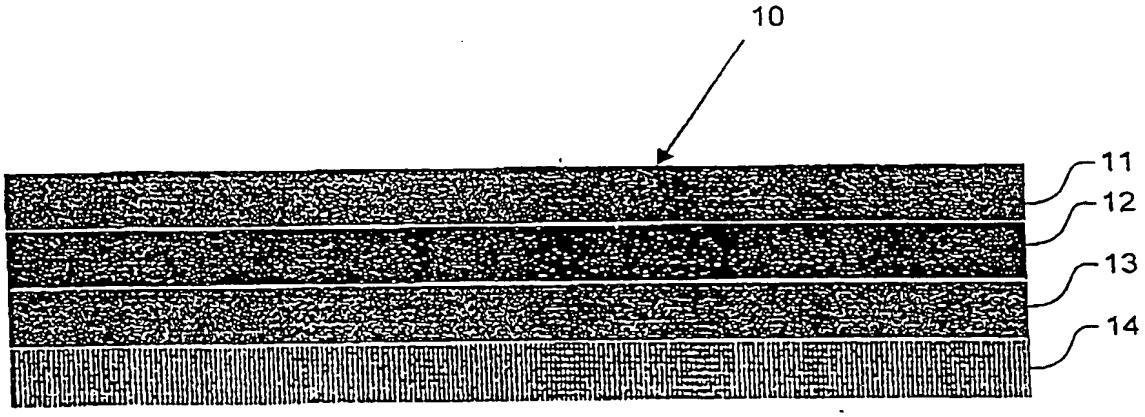


FIGURE 1

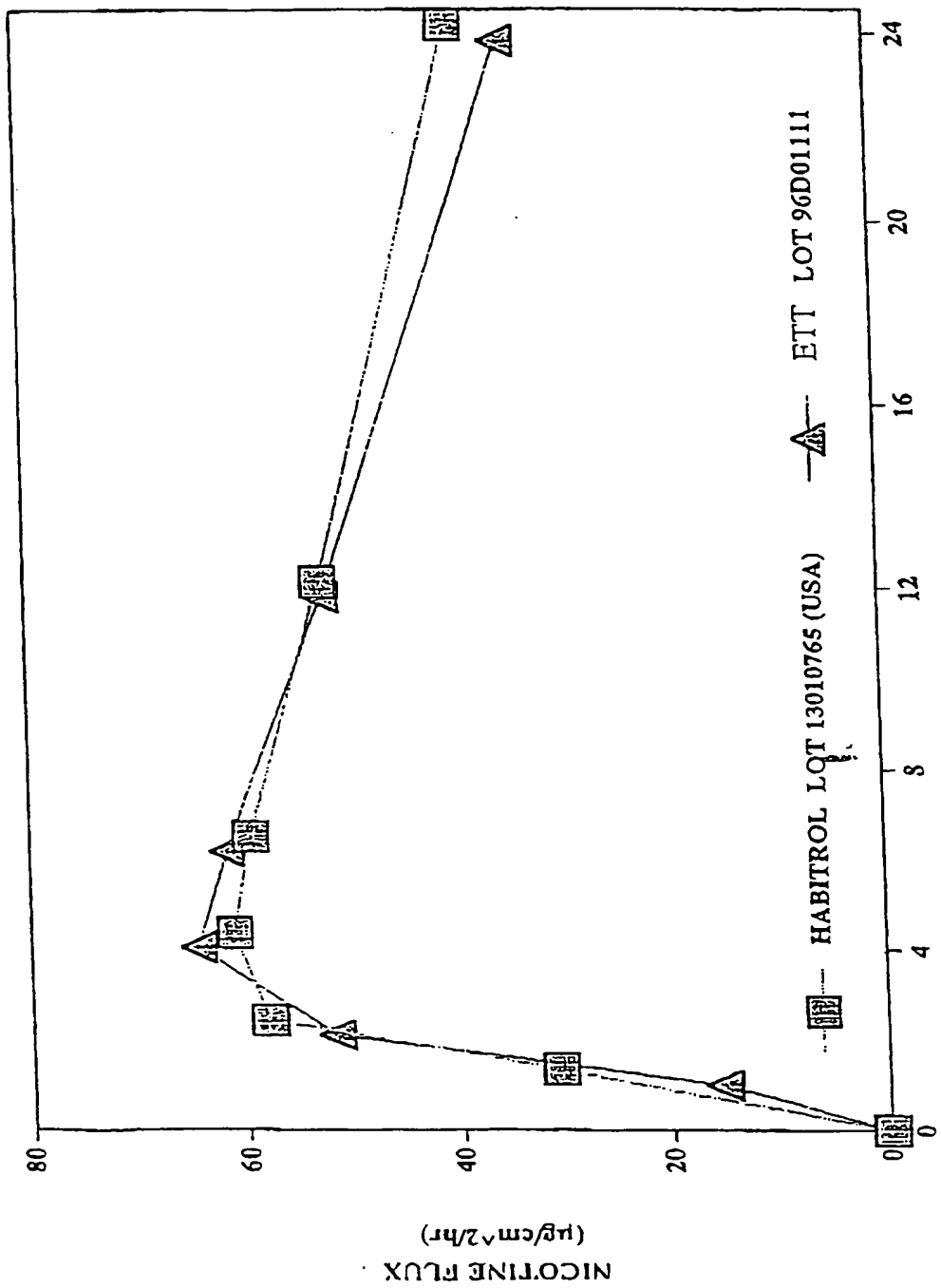

NICOTINE FLUX
(μg/cm^2/hr)
80
60
40
20
0
0
4
8
12
16
20
24
TIME (Hours)
HABITROL LOT 13010765 (USA)
ETT LOT 96D01111

FIGURE 2

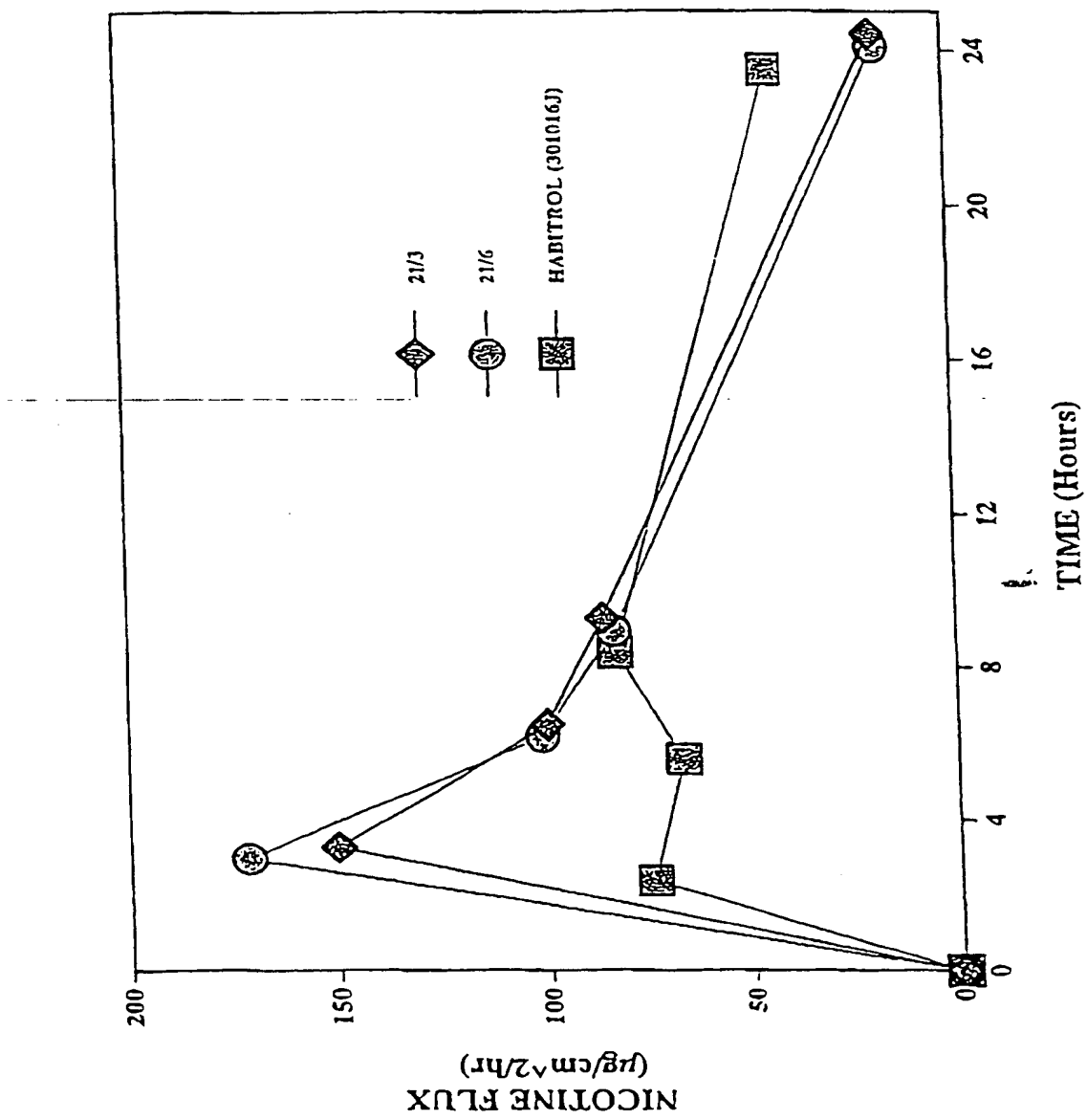

NICOTINE FLUX
(μg/cm^2/hr)
200
150
100
50
0
0
4
8
12
16
20
24
TIME (Hours)
21/3
21/6
HABITROL (301016J)

FIGURE 3

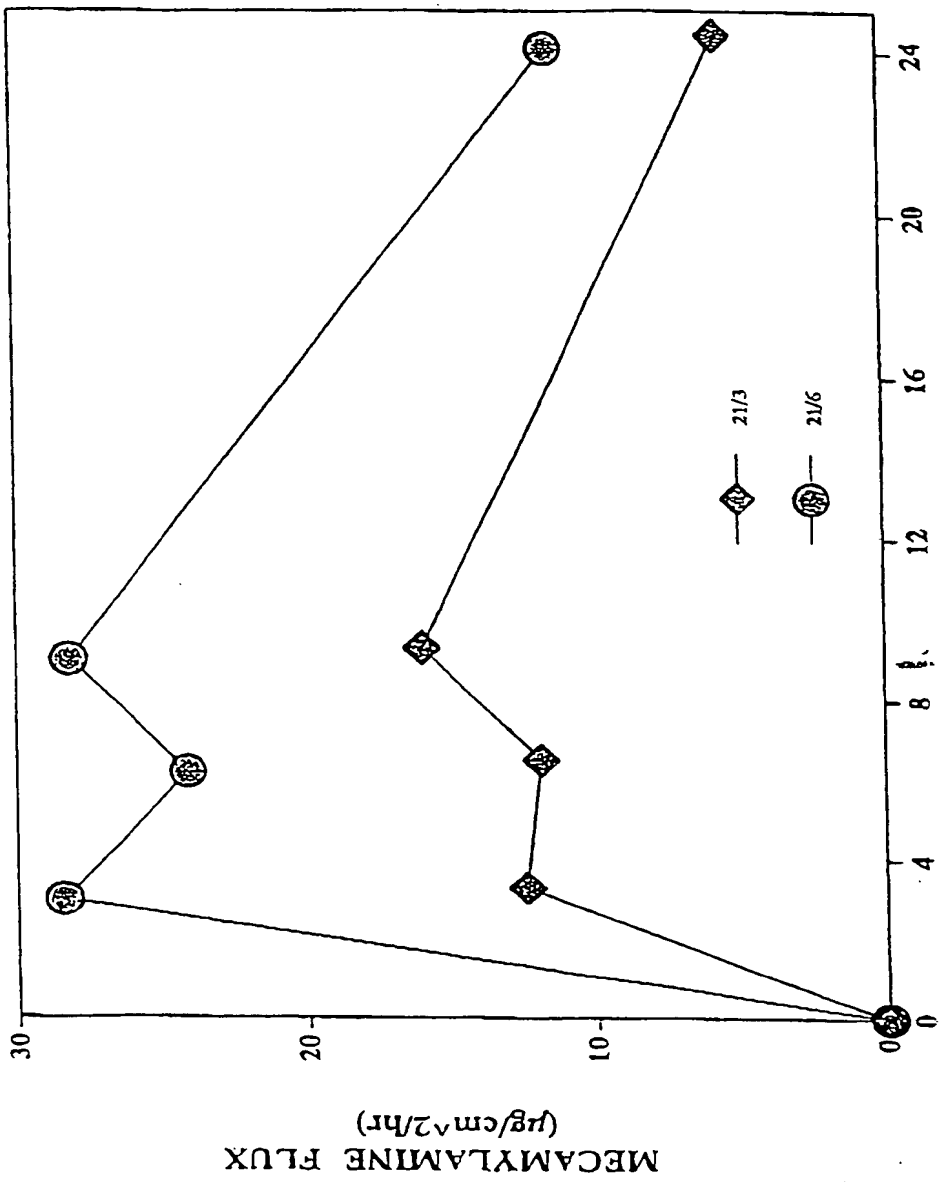

MECAMYLAMINE FLUX
(μg/cm^2/hr)
30
20
10
0
0
4
8
12
16
20
24
TIME (Hours)
21/3
21/6

FIGURE 4

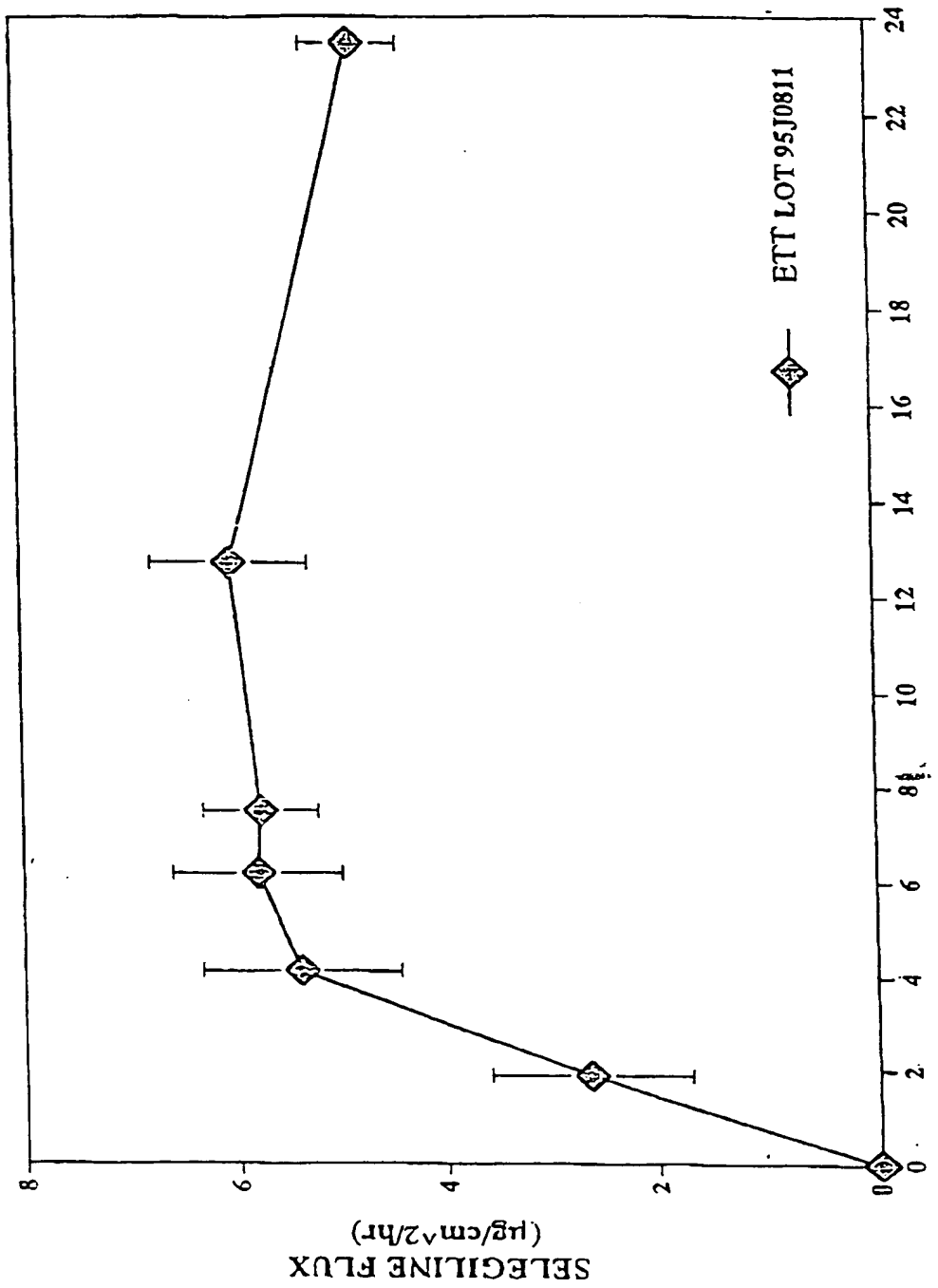

SELEGILINE FLUX
(μg/cm^2/hr)
0
2
4
6
8
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (Hours)
ETT LOT 95J0811

FIGURE 5

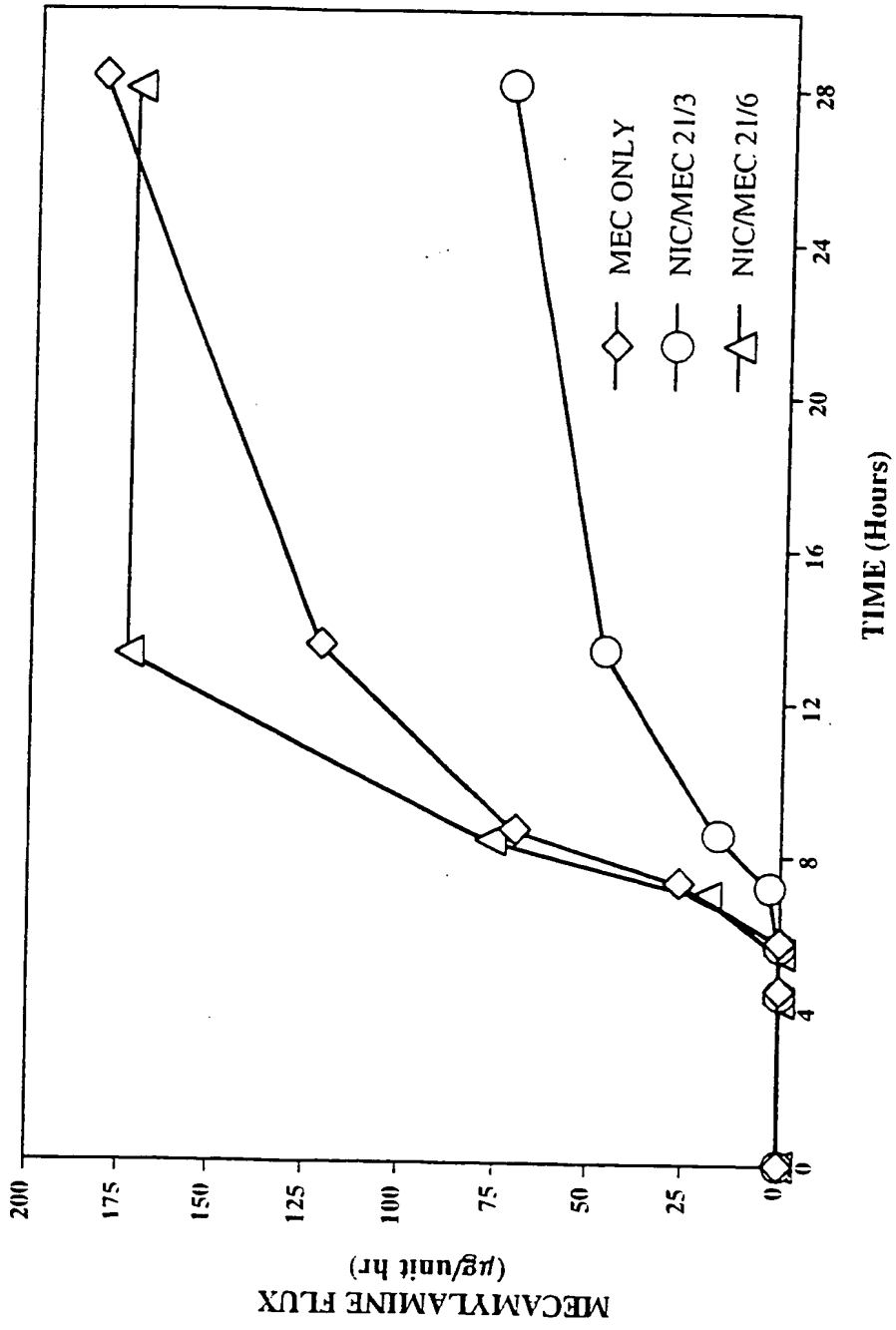
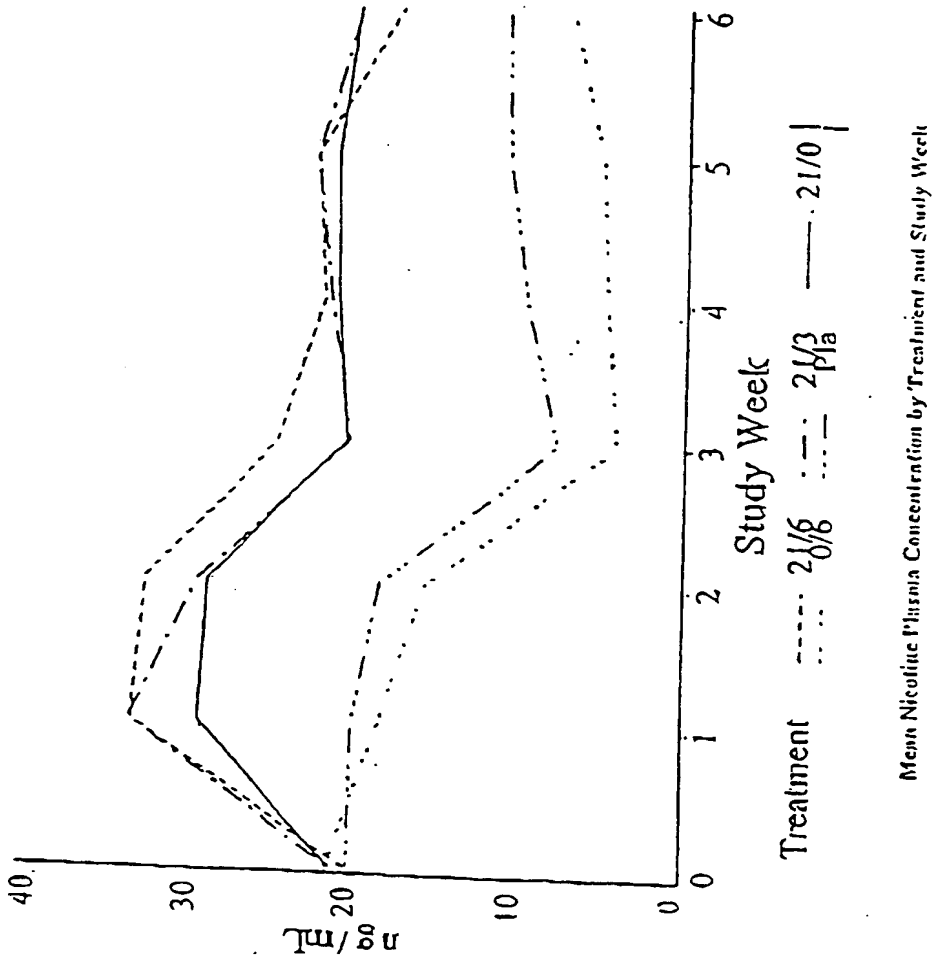

MECAMYLAMINE FLUX
(μg/unit hr)
200
175
150
125
100
75
50
25
0
0
4
8
12
16
20
24
28
TIME (Hours)
MEC ONLY
NIC/MEC 21/3
NIC/MEC 21/6

FIGURE 6



Mean Nicotine Plasma Concentration by Treatment and Study Week

FIGURE 7

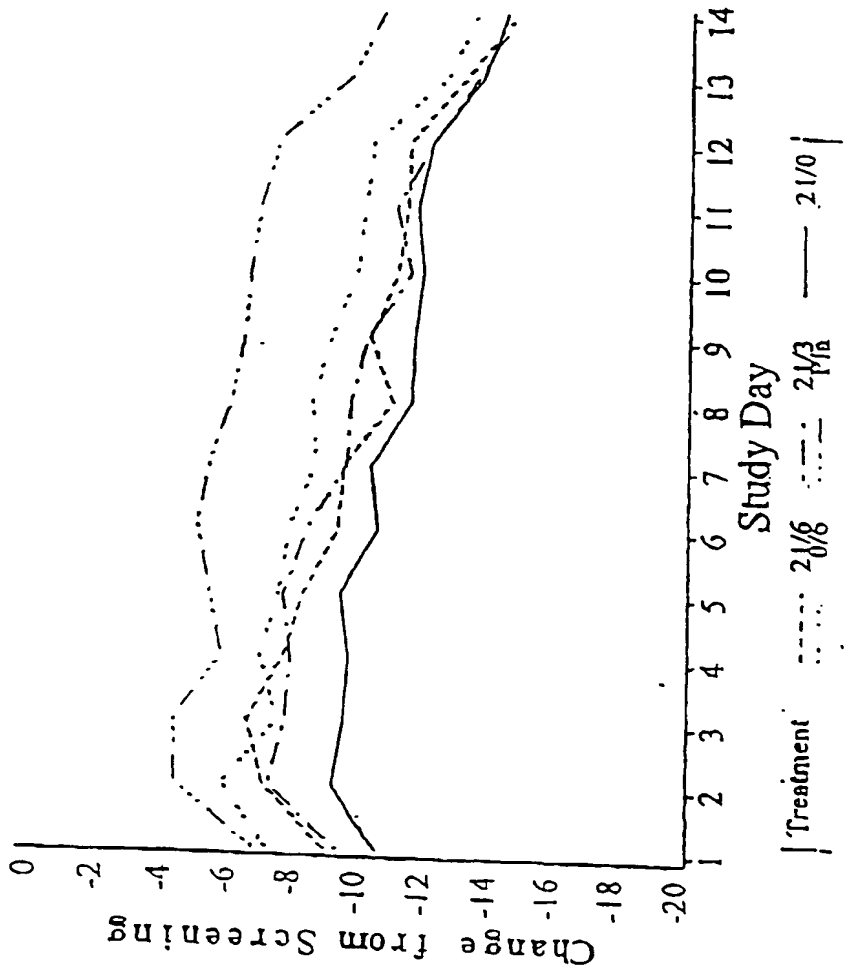

Change from Screening
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Study Day
Treatment
21/6
21/3
21/0
Mean Observed Change in Number of Cigarettes by Treatment and Day

FIGURE 8

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(51) International Patent Classification 7 :
A61K 9/70, 31/465, 31/137, 31/131, C07D 401/04, C07C 211/27, 211/36

A3

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(71) Applicant *(for all designated States except US)*: ELAN CORPORATION, PLC [IE/IE]; Lincoln House, Lincoln Place, 2 Dublin (IE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MIRANDA, J. [US/US]; Elan Transdermal Technologies, 3250 Commerce Parkway, Miramar, FL 33025 (US). BETLACH, C., J., II [US/US]; Elan Transdermal Technologies, 3250 Commerce Parkway, Miramar, FL 33025 (US).

(74) Agents: BEARD, Collen, A. et al.; Jones & Askew, LLP, 2400 Monarch Tower, 3424 Peachtree Road, N.E., Atlanta, GA 30326 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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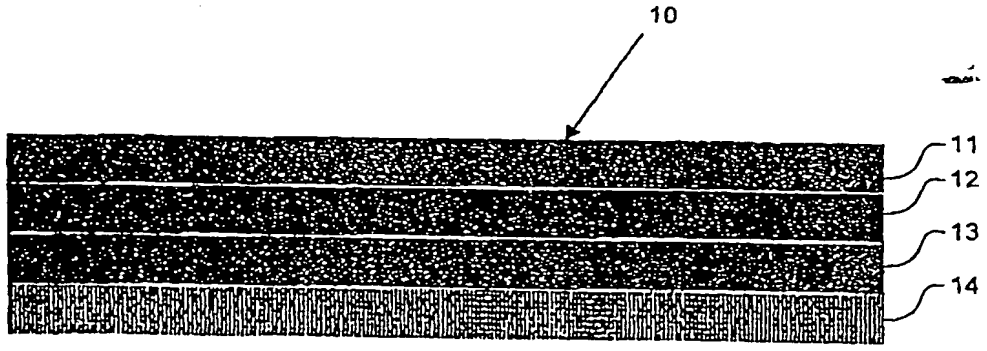
23 November 2000 (23.11.00)

(54) Title: TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS



(57) Abstract

A transdermal patch for administering a volatile liquid drug, such as nicotine, transdermally to a patient comprising a four-layer laminated composite of: a top drug impermeable backing layer; a pressure sensitive silicone adhesive layer containing the drug; a pressure sensitive acrylic adhesive layer also containing the drug; and a removable siliconized release liner layer. Also disclosed is a method for treating a person for nicotine dependence and particularly for treating a woman for nicotine dependence.

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INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 99/28697

A. CLASSIFICATION OF SUBJECT MATTER

A61K9/70,A61K31/465,A61K31/137,A61K31/131,C07D401/04,
C07C211/27,C07C211/36

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Minimum documentation searched (classification system followed by classification symbols)

A61K,C07D,C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/40085 A (NOVEN PHARMACEUTICALS, INC.) 19 December 1996, page 8, line 14 - page 9, page 18, line 32 - page 19, line 2, page 19, lines 18-37, examples 2-4, claims 1,3-6, 9,10,17,19-21,24.	1,2, 4,6-8, 10,11, 13
Y	--	3,5
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Y	--	3,5
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Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2000	27. 06. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	KRENN e.h.

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INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/US 99/28697

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indicaton, where appropriate, of the relevant passages	Relevant to claim No.
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ANHANG

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

To the International Search Report to the international Patent Application No.

ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/US 99/28697 SAE 268121

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ANHANG

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

To the International Search Report to the international Patent Application No.

ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/US 99/28697 SAE 268121

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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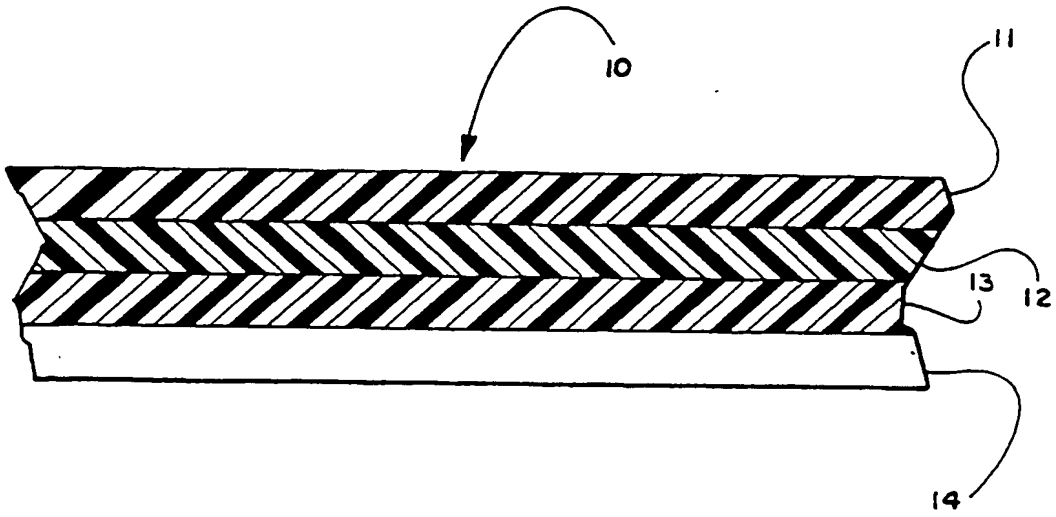
(54) Title: TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS



(57) Abstract: A transdermal patch for administering a volatile liquid drug, such as nicotine, transdermally to a patient comprising a four-layer laminated composite of: a top drug impermeable backing layer; a pressure sensitive silicone adhesive layer containing the drug; a pressure sensitive acrylic adhesive layer also containing the drug; and a removable siliconized release liner layer. Also disclosed is a method for treating a person for nicotine dependence and particularly for treating a woman for nicotine dependence.

WO 00/33812 A3

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS

TECHNICAL FIELD

This invention is in the field of transdermal drug delivery devices. More particularly, it relates to a method for making transdermal patches that deliver volatile liquid drugs, such as nicotine, mecamylamine and selegiline, and to the resulting patches. The invention also relates to a method for treating a person for nicotine dependence comprising transdermally administering an effective amount of mecamylamine to the person without transdermal coadministration of nicotine. The invention further relates to a method for treating women for nicotine dependence comprising transdermally co-administering effective doses of mecamylamine and nicotine.

BACKGROUND ART

There are two basic types of transdermal patches that are used to deliver liquid drugs. One is a liquid reservoir patch in which the liquid drug, either neat or dissolved in a carrier, is confined in a pouch or sac within the device. An example of such a device for delivering nicotine is shown in Fig. 1 of U.S. Pat. No. 5,364,630. The other is a matrix patch in which the liquid drug is dissolved in one or more polymeric layers of a laminated composite. Examples of matrix patches that deliver nicotine are described in U.S. Pat. No. 5,603,947. The present invention relates to a matrix patch.

In the manufacture of matrix patches for administering volatile liquid drugs such as nicotine it is common to attempt to avoid steps involving heat treatment, e.g., drying, so as to avoid excessive loss or degradation of the drug. For instance U.S. Pat. No. 4,915,950 and 5,603,947 describe a printing procedure whereby neat nicotine is applied to a nonwoven fabric laminated to a polyisobutylene adhesive layer. Alternatively "hot" melt adhesives that melt at relatively low temperatures have been used as a matrix material for these drugs. See U.S. Pat. No. 5,411,739.

PCT Pub. No. WO 96/40085 describes transdermal matrix patches for administering drugs such as selegiline, nitroglycerin and nicotine, that are liquid at normal room temperature. The publication suggests making a monolithic matrix of the drug in an adhesive by mixing one

or more polymeric adhesives, preferably polyacrylate and polysiloxane, and the drug in a volatile solvent, casting the mixture, and evaporating the solvent. The publication lists as examples of volatile solvents isopropanol, ethanol, xylene, toluene, hexane, cyclohexane, heptane, ethyl acetate and butyl acetate.

When silicone adhesives have been used as the matrix material in nicotine patches the matrix layer has been cast from a heptane solution. See, for instance, Example 1 of U.S. Pat. No. 5,603,947. Other co-solvents, including hexane, have been suggested for use with silicone adhesives used in transdermal devices. See p. 3, line 51, et seq. of EPO 524776 A1.

Mecamylamine is an antagonist to nicotine. U.S. Patent Nos. 5,316,759, 5,726,190, and 5,574,052 teach the coadministration of mecamylamine and nicotine to treat nicotine dependency. These patents do not teach or suggest the transdermal administration of mecamylamine itself to treat nicotine dependency. Furthermore, the prior art does not teach that coadministration of mecamylamine and nicotine is especially effective as a smoking cessation aid specifically suited for women.

DISCLOSURE OF THE INVENTION

One aspect of this invention is a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) a top backing layer that is impermeable to the drug;

b) silicone adhesive layer containing the drug and underlying the backing layer;

c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and

d) a removable release liner layer underlying the acrylic adhesive layer, wherein the combined amount of drug in the silicone adhesive layer and the acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.

Another aspect of the invention is a method of making a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;

b) evaporating the hexane from the coating to form a silicone adhesive layer containing the drug; and

c) laminating a polyacrylate adhesive layer affixed to a release liner layer onto the silicone adhesive layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.

Another aspect of the invention is a method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal coadministration (or other coadministration except by smoking) of nicotine to the person.

A further aspect of the invention is a method for treating a woman for nicotine dependence comprising transdermally coadministering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a elevational cross-sectional view of an embodiment of the invention patch.

Figures 2-6 are graphs of the results of the *in vitro* skin flux tests described in the examples.

Figures 7 and 8 are graphs of the results of the clinical studies described in the examples.

MODES FOR CARRYING OUT THE INVENTION

As used herein the term "volatile liquid drug" intends a drug that (i) is capable of permeating through unbroken human skin at therapeutically effective rates from a patch of practical size, the permeation either being unenhanced or enhanced through coadministration of one or more skin permeation enhancing agents, (ii) is a liquid at 25°C, atmospheric pressure, and (iii) has a boiling point less than about 300°C at atmospheric pressure. Examples of such drugs are nicotine, mecamylamine, selegiline, and nitroglycerine.

As used herein the term "diffusional contact" intends a relationship, either through direct contact or through indirect contact via an intermediary material, between two surfaces or layers such that drug is able to pass by diffusion from one surface or layer to the other surface or layer.

As used herein the term "treating a person for nicotine dependence" intends causing the person to reduce or eliminate his or her intake of nicotine from smoking and/or chewing tobacco on a temporary or permanent basis.

The embodiment of the invention shown in Figure 1 is a four-layer laminated composite matrix type transdermal patch, generally designated 10. The four layers are: (1) a top drug-impermeable backing layer 11; (2) an intermediate drug-containing silicone adhesive layer 12; (3) a basal drug-containing polyacrylic adhesive layer 13; and (4) a removable release liner layer 14.

Materials for making backing layer 11 are well known in the art. They include various polymers such as polyethylene terephthalate, polyethylene, polypropylene and polyvinyl chloride, metal foils such as aluminum foil, and polymer-metal composites.

Adhesive layer 12 is made from a pressure sensitive silicone adhesive. An amine compatible silicone adhesive is preferred for use with drugs, such as nicotine, which contain amine groups. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989). See also Pfister, W.R., et al. "Silicon Adhesives for Transdermal Drug Delivery" Chemistry in Britain (Jan. 1991), pp. 43-46 and EP Pub. No. 0524776 A1. Suitable commercially available silicone pressure sensitive adhesives are available from Dow Corning under the trademark BIO-PSA. The silicone pressure sensitive adhesives are supplied commercially as solutions in a solvent. Per the present invention the solvent should be hexane. The thickness of layer 12 will usually be in the range of about 25 to 100 microns, more usually 50 to 75 microns. Expressed alternatively, the layer 12 will be present at about 4 to 18 mg/cm^2, more usually 8 to 14 mg/cm^2. Adhesive layer 12 initially (before it is laminated to adhesive layer 13) contains the entire drug loading. In this regard, the drug(s) will usually be added to the silicone adhesive in amounts ranging between about 5% to 50% by weight, more usually 10% to 30% by weight, based on the total dry weight of drug and adhesive.

Adhesive layer 13 is made from one or more solution acrylic pressure sensitive adhesives. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 396-456 (D. Satas, ed.) Van Nostrand Reinhold, New

York (1989). They are usually copolymers composed of: 50% to 90% of a main acrylate or methacrylate monomer, usually 2-ethylhexyl acrylate, butylacrylate, or iso-octyl acrylate; 10% to 40% of a modifying monomer such as vinyl acetate; and 2% to 20% of a functional group-containing monomer such as acrylic acid. Examples of suitable commercially available solution acrylic pressure sensitive adhesives are: National Starch DuroTak® adhesives 87-2194 and 87-2070. The thickness of the acrylic adhesive layer 13 will usually be about the same as that of layer 12. After lamination to the silicone adhesive layer 12 and equilibration of the drug between layers 12 and 13, layer 13 will also contain drug. In this regard the drug will usually constitute about 2.5% to 30% by weight, preferably 5% to 15% by weight, of layer 13 after equilibration occurs.

The release liner layer 14 is removed before device 10 is placed on the skin. After layer 14 is removed the lower surface of layer 13 is exposed and defines the basal surface of the device which is intended to be placed directly in contact with the skin. Release liner layers are well known in the transdermal patch art. They are made of materials that permit the layer to be easily stripped or peeled away from the adjacent pressure sensitive adhesive layer. Release liner layers are typically made from drug impermeable polymers such as polyesters which are coated with materials such as silicone or fluorinated hydrocarbons that reduce the adhesiveness between it and the adjacent pressure sensitive adhesive layer. In this regard since the acrylic pressure sensitive adhesive layer rather than the silicone pressure sensitive adhesive layer defines the basal surface of the device it is possible to use a siliconized release liner. Such liners are generally not compatible with silicone adhesives. Siliconized liners are more economical than fluorocarbon coated liners. Further, use of the acrylic pressure sensitive adhesive as the basal layer provides a more controlled and predetermined delivery of the drug than could be achieved using a silicone adhesive basal layer. The particular drug release profile from the patch can be varied by altering the thickness and/or composition of the acrylic pressure sensitive adhesive layer and/or the drug loading, and/or by employing a permeation enhancer.

The drug is released from the surface of the acrylic pressure sensitive adhesive to the skin at a therapeutically effective rate. That rate will depend upon the particular drug. In the case of nicotine, the rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr. In the case of co-administration of nicotine and the mecamylamine, the nicotine rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr, and the mecamylamine rate will usually be in the range of 0.02 to 1 mg/hr, preferably 0.1 to 0.6 mg/hr. In the case of

mecamylamine alone, the rate will usually be in the range of 0.02 to 1 mg/hr, preferably 0.1 to 0.6 mg/hr. In the case of selegiline, the rate will usually be in the range of 0.2 to 3 mg/day. The flux (rate per unit area) of drug from the basal surface of the acrylic pressure sensitive adhesive and the area of that surface are matched to provide the desired rate of drug administration. As indicated, the flux may be varied by altering the drug loading, composition and/or thickness of the acrylic pressure sensitive adhesive layer, and/or by the use of permeation enhancers. The surface area of the layer in diffusional contact with the skin will usually be in the range of 5 to 100 cm^2, more usually in the range of about 10 to 50 cm^2. Each patch may be applied to the skin for periods of from several hours up to about a week, and more preferably for about 1 to 3 days.

The patches of the invention are made in the following manner. The drug(s) is dissolved in the desired proportion(s) in a hexane solution of the pressure sensitive silicone adhesive. The drug(s) will normally constitute about 2.5% to 25% by weight of the solution. This solution is then cast onto the backing layer and allowed to dry. By casting the drug and silicone adhesive from a hexane solution, very low casting and drying temperatures (30°C to 40°C) may be used, thus reducing degradation or loss of the liquid drug(s) during the casting and drying process. Even though low processing temperatures in the 30°C to 40°C range are used, low residual hexane levels (e.g., < 0.1 % by wt.) are found in the layer after about 1 to 5 min. of drying. Other solvents, such as heptane and toluene, are not suitable since they require higher processing temperatures and thus result in more drug degradation and/or evaporation during coating and drying. Other pressure sensitive adhesives such as acrylics or polyisobutylenes are similarly not suitable for formulating liquid drugs since they require higher processing temperatures to remove their solvents (e.g., ethyl acetate, heptane, etc.). The silicone adhesive also has excellent adhesion to the backing. A solution of the acrylic pressure sensitive adhesive is cast onto a siliconized release liner layer and permitted to dry. The acrylic pressure sensitive adhesive/release liner subassembly is then laminated to the drug-containing silicone pressure sensitive adhesive/backing subassembly to form the final laminated composite. After lamination the drug(s) equilibrates in the adjacent adhesive layers. Patches are cut/punched from the composite and placed in appropriate packaging.

Alternatively, the drug and silicone adhesive solution can be cast onto a disposable liner and dried as described. The sub-assembly can be laminated to the acrylic pressure sensitive adhesive/release liner subassembly. The disposable liner is then removed to expose the top surface of the silicone adhesive layer. A backing is then laminated to the top surface of the

silicone adhesive layer to form the final laminated composite. In still another alternative manufacturing scheme, the solution of silicone adhesive and drug is cast directly into the acrylic pressure sensitive adhesive release liner subassembly and dried. A backing is then applied to form the completed laminated composite.

It has surprisingly been found that, in the treatment of nicotine dependence, women respond more favorably to a patch that combines nicotine and mecamylamine than to a patch that contains either nicotine or mecamylamine alone. The patch can be administered while the woman continues to smoke and then ceases smoking or if she chooses to stop smoking at the same time as beginning treatment.

For treatment of nicotine dependence, the patches of the invention are typically worn for a total period of about 3 to 16 weeks. During the first 1 to 4 weeks, preferably 2 to 3 weeks, the patent is allowed to smoke as desired. During the remainder of the treatment, i.e., two to 12 weeks, preferably 4 to 8 weeks, the patient is advised to not smoke.

EXAMPLES

The following examples further illustrate the patches of the invention and the process used to make them. These examples are not intended to limit the invention in any manner.

Example 1: Preparation and Testing of Nicotine Patch

Nicotine was added to a hexane solution of Dow Corning BIO-PSA amine-compatible silicone pressure sensitive adhesive to a level of approximately 12% by weight based on the combined dry weight of adhesive and nicotine. The resulting hexane solution of adhesive and nicotine was coated onto a 3M Scotchpak 1109 polyester/polyolefin backing at 13.8 mg/cm^2 (1.63 mg/cm^2 nicotine and 12.17 mg/cm^2 adhesive) and the coated backing was dried at 30°C to 40°C for about 3 min.

National Starch DuroTak 87 2194 acrylic solution pressure sensitive adhesive was coated onto a 125 micron thick Daubert Coater Products 1-5 PESTR (Matte) - 164Z siliconized polyester release liner at 13.18 mg/cm^2 and the coated release liner was dried at 100°C for about 10 min.

The dried silicone adhesive/nicotine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the nicotine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of nicotine within the layers was about 6% (w/w) after equilibration.

In vitro nicotine flux from the laminated composite was determined at 32°C through human cadaver epidermis into an infinite sink using modified Franz glass diffusion cells. Nicotine assays were made by HPLC.

For comparison purposes the flux of nicotine from commercial Habitrol3 21 mg/day patches was determined using the same test procedure. Figure 2 is a graph of the nicotine flux from the composite of the example and from the Habitrol3 patches versus time.

Example 2: Preparation and Testing of Nicotine/Mecamylamine Patches

Nicotine and mecamylamine were added to a hexane solution of Dow Corning BIO-PSA amine compatible silicone pressure sensitive adhesive. Two batches were made: one contained approximately 10% nicotine and 6.4% mecamylamine based on the total dry weight of the adhesive and the two drugs; and a second contained approximately 10% nicotine and 4.2% mecamylamine, based on the total dry weight of the adhesive and the two drugs. The batches were separately coated onto a 3M Scotchpak 1109 polyester/polyoefin backing film at 9.6 mg/cm^2 (0.96 mg/cm^2 nicotine, 0.61 mg/cm^2 mecamylamine, 8.03 mg/cm^2 adhesive for the first batch; 0.96 mg/cm^2 nicotine, 0.40 mg/cm^2 mecamylamine, 8.24 mg/cm^2 adhesive for the second batch) and then dried at 30 to 40°C for about 2 min.

A blend of two National Starch DuroTak acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w, respectively, was made. The blend was coated at 8.0 mg/cm^2 onto a 75 micron thick Daubert Coater Products siliconized polyester release liner (1-3 PESTR (Matte) - 164Z) and dried at about 100°C for about 10 min.

The drug-containing silicone adhesive/backing subassembly was then laminated to the acrylic adhesive/release liner subassembly to form a four layer/laminated composite. After lamination the nicotine and mecamylamine distributed themselves uniformly within the adjacent

adhesive layers. The concentration of the drugs in the adhesive layers after equilibration was: nicotine, 5.45% (w/w) and mecamylamine 3.47% (w/w) for the composite made from the first batch and 5.45% (w/w) and 2.27% (w/w), respectively, for the composite made from the second batch. Patches about 23 cm^2 in area were cut from the composites. These patches were designed to deliver 21 mg of nicotine and 6 mg of mecamylamine in 24 hr and 21 mg of nicotine and 3 mg of mecamylamine in 24 hr, respectively.

Nicotine and mecamylamine fluxes from the patches were determined using the procedure described Example 1. Mecamylamine assays were made by GC. Figure 3 is a graph showing the nicotine flux from the patches versus time. Patches made from the first batch composite are designated 21/6; those from the second batch composite are designated 21/3. Figure 4 similarly is a graph showing the mecamylamine flux from the patches.

Example 3 Preparation and Testing of Selegiline Patch

Selegiline was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 10% by weight based on the combined dry weight of adhesive and selegiline. The resulting hexane solution of adhesive and selegiline was coated on 3M Scotchpak 1109 polyester/polyolefin backing at 10.0 mg/cm^2 (1.0 mg/cm^2 selegiline and 9.0 mg/cm^2 adhesive) and the coated backing was dried at 30°C to 40°C for about 3 minutes.

National Starch DuroTak® 87-2194 acrylic solution pressure sensitive adhesive was coated onto a 125 micron thick Daubert Coated Products 1-5 PESTER (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm^2 and the coated release liner was dried at about 100°C for about 10 minutes.

The dried silicone adhesive/selegiline-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the selegiline distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of selegiline within the layers in about 5.5% (w/w) after equilibration.

Selegiline flux from the patches was determined using the procedure described in Example 1. Selegiline assays were made by HPLC.

Figure 5 is a graph of the selegiline flux from the composite of this example versus time.

Example 4. Preparation and Testing of Mecamylamine Patch

Mecamylamine was added to a hexane solution of Dow Corning BIO-PSA® amine-compatible silicone pressure sensitive adhesive to a concentration of approximately 6.3% by weight based on the combined dry weight of adhesive and mecamylamine. The resulting hexane solution of adhesive and mecamylamine was coated on 3M Scotchpack 1109 polyester/polyolefin backing at 9.6 mg/cm^2 (0.61 mg/cm^2 mecamylamine and 8.99 mg/cm^2 adhesive) and the coating backed was dried at 30°C to 40°C for about 3 minutes.

A blend of two National Starch DuroTak® acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w, respectively, was made. The blend was coated onto a 75 micron thick Daubert Coated Products 1-2 PESTR (Matte)-164Z siliconized polyester release liner at 8.0 mg/cm^2 and the coated release liner was dried at about 100°C for about 10 minutes.

The dried silicone adhesive/mecamylamine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the mecamylamine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of mecamylamine within the layers is about 3.47% (w/w) after equilibration. Patches about 23 cm^2 in area were cut from the composites. These patches were designed to deliver 6 mg of mecamylamine in 24 hr.

Mecamylamine flux from the patches was determined using the procedure described in Example 1. The mecamylamine assay was done by gas chromotography. Figure 6 is a graph of the mecamylamine flux from the composite of this example versus time; mecamylamine flux through the same section of cadaver skin from the 21/3 and 21/6 compositions of Example 2 are shown for comparison.

Study A.

Patches made according to Examples 1, 2 and 4 and a placebo patch were subject to a clinical study. The study was a multi-center, double-blind, randomized parallel group study. Patients were randomized to receive one of five treatments: nicotine/mecamylamine 21/6; nicotine/mecamylamine 21/3; nicotine (21 mg/24 hr); mecamylamine (6 mg/24 hr) and placebo. Patches were applied daily for the first six weeks of the study. Patients were instructed to continue smoking for the first two weeks and to stop smoking thereafter.

Among the efficacy parameters monitored during the study were four week continuous abstinence after the quit smoking date, nicotine plasma concentration, and ad hoc smoking during the treatment period.

Table 1 below provides the overall abstinence data for the study. In the table "N" represents the number of patients, "No" indicates non-abstinence and "Yes" indicates abstinence. As indicated the nicotine/mecamylamine 21/6 gave the highest abstinence.

Table 1

	Overall	21/6	21/3	21/0	0/6	Pla
N	705	142	141	141	140	141
No	82%	74%	79%	79%	82%	92%
Yes	18%	26%	21%	21%	18%	8%

Figure 7 is a graph showing the mean nicotine plasma concentrations in ng/ml of the patients by treatment and time. As shown, the mecamylamine only patch (0/6) produced a steady decline in nicotine levels even during the initial two-week period of the study. Fig. 8 is a graph showing the mean observed change in the number of cigarettes smoked by treatment and day. Surprisingly, the number of cigarettes smoked did not increase with the mecamylamine only (0/6) treatment, as the literature reports that oral mecamylamine administration increased ad hoc cigarette consumption.

Study B.

A second multi-center, double-blind, randomized parallel group clinical study was conducted. Patients were randomized to receive one of three treatments: nicotine/mecamylamine 21/6; nicotine/mecamylamine 21/3, and nicotine (21 mg/24 hr). Patient instructions were the same as in the first study.

The abstinence data for this study are summarized in Table 2. In this study the nicotine/mecamylamine combination was again more effective than nicotine alone.

Table 2

Treatment	21/6	21/3	21/0
N	180	180	180
Abstinence	29%	29%	23%

A detailed examination of the data the clinical studies yielded a surprising difference in abstinence rates for females and males. In both studies, the abstinence rate for females in the 21/6 treatment group was 31% compared to the 21/0 treatment group rates of 17% in the first study and 18% in the second study. These gender specific data are summarized in Table 3.

Table 3

Study	Gender		21/6	21/3	21/0	0.6	Plac
First	Female	N	70	67	63	75	74
		% Abst.	31	16	17	17	9
	Male	N	72	74	78	65	67
		% Abst.	21	26	24	18	6
Second	Female	N	93	96	91		
		% Abst.	31	29	18		
	Male	N	87	84	89		
		% Abst.	28	29	28		

N = number of subjects in study.

% Abst.= Four-week continuous abstinence results.

Modifications of the above described modes for carrying out the invention that are obvious to persons of skill in the transdermal patch art are intended to be within the scope of the following claims. All publications, patent applications and patents noted above are hereby incorporated by reference.

CLAIMS

1. A transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) a top backing layer that is impermeable to the drug;

b) an intermediate silicone adhesive layer containing the drug and underlying the backing layer;

c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and

d) a removable release liner layer underlying the acrylic adhesive layer,

wherein the combined amount of drug in the silicone adhesive layer and acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.

2. The transdermal patch of claim 1, wherein the drug is nicotine and the patch is capable of administering 0.2 to 1.5 mg nicotine per hour to the patient.

3. The transdermal patch of claim 1, wherein the drug is a combination of nicotine and mecamylamine and the patch is capable of administering 0.2 to 1.5 mg nicotine per hour and 0.02 to 1 mg mecamylamine per hour to the patient.

4. The transdermal patch of claim 1 wherein the drug is selegiline and the patch is capable of administering 0.2 to 3 mg selegiline per day to the patient.

5. The patch of claim 1 wherein the drug is mecamylamine only and the patch is capable of administering 0.02 to 1 mg mecamylamine per hour to the patient.

6. The patch of claim 1 wherein the release liner layer is a siliconized release liner layer.

7. The patch of claim 1 wherein the acrylic adhesive layer is made from a blend of two acrylic adhesives.

8. A method of making a transdermal patch for administering a volatile liquid drug to a patient comprising:

a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;

b) evaporating the hexane from the coating to form a layer of drug-containing silicone adhesive on the backing layer; and

c) laminating an assembly comprising an acrylic adhesive coated onto a release liner layer onto the silicone adhesive layer on the backing layer such that the silicone adhesive layer and the acrylic adhesive layer are in diffusional contact with each other.

9. The method of claim 8 wherein step b) is carried out at 30°C to 40°C.

10. The method of claim 8 wherein the release liner layer is a siliconized release liner layer.

11. The method of claim 8 wherein the drug is nicotine.

12. The method of claim 8 wherein the drug is a combination of nicotine and mecamylamine.

13. The method of claim 8 wherein the drug is selegiline.

14. The method of claim 8 wherein the drug is mecamylamine only.

15. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine without transdermal co-administration of nicotine to the person.

16. The method of claim 15 wherein the rate of mecamylamine administration is 0.02 to 1 mg/hr.

17. The method of claim 15 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr.

18. A method for treating a person for nicotine dependence comprising transdermally administering a therapeutically effective amount of mecamylamine to the person for a first time period during which the person smokes cigarettes as desired and continuing said administration for a second time period during which the person is advised to not smoke.

19. The method of claim 18 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.

20. The method of claim 18 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.

21. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman.

22. The method of claim 21 wherein the rate of mecamylamine administration is 0.02 to 1 mg/hr and the rate of nicotine administration is 0.2 to 1.5 mg/hr.

23. The method of claim 21 wherein the rate of mecamylamine administration is 0.1 to 0.6 mg/hr and the rate of nicotine administration is 0.3 to 0.9 mg/hr.

24. A method for treating a woman for nicotine dependence comprising transdermally co-administering a therapeutically effective amount of nicotine and a therapeutically effective amount of mecamylamine to the woman for a first time period during which the woman smokes cigarettes as desired and continuing said administration for a second time period during which the woman is advised to not smoke.

25. The method of claim 24 wherein the first time period is about 1 to about 4 weeks and the second time period is about 2 to about 12 weeks.

26. The method of claim 24 wherein the first time period is about 2 to about 3 weeks and the second time period is about 4 to 8 weeks.

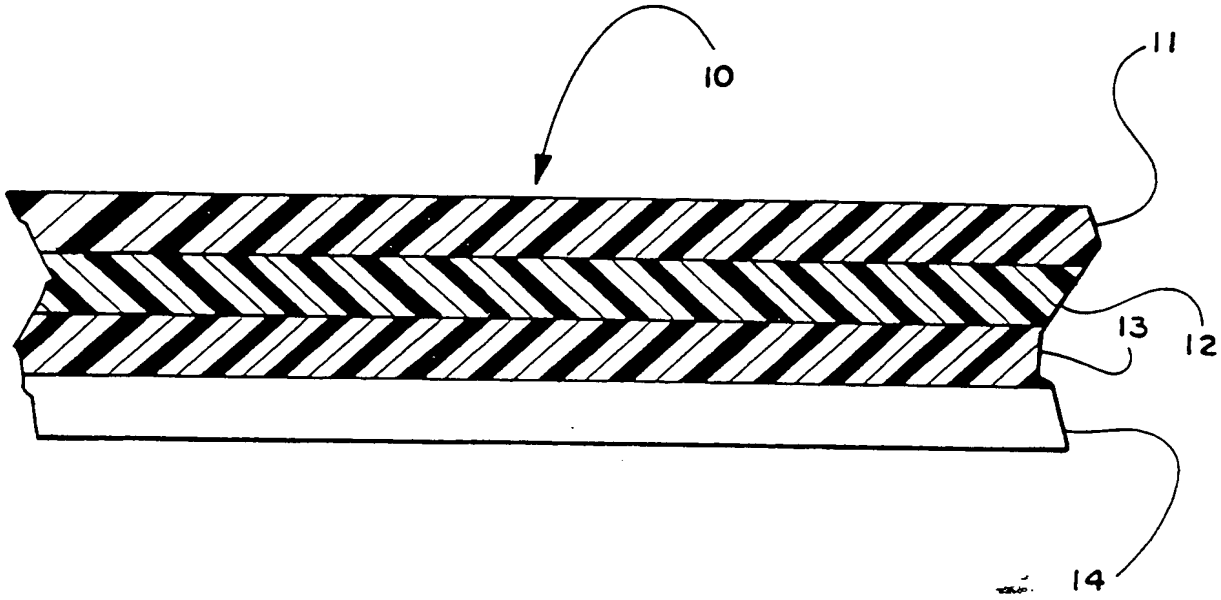


Fig. 1

Fig. 2

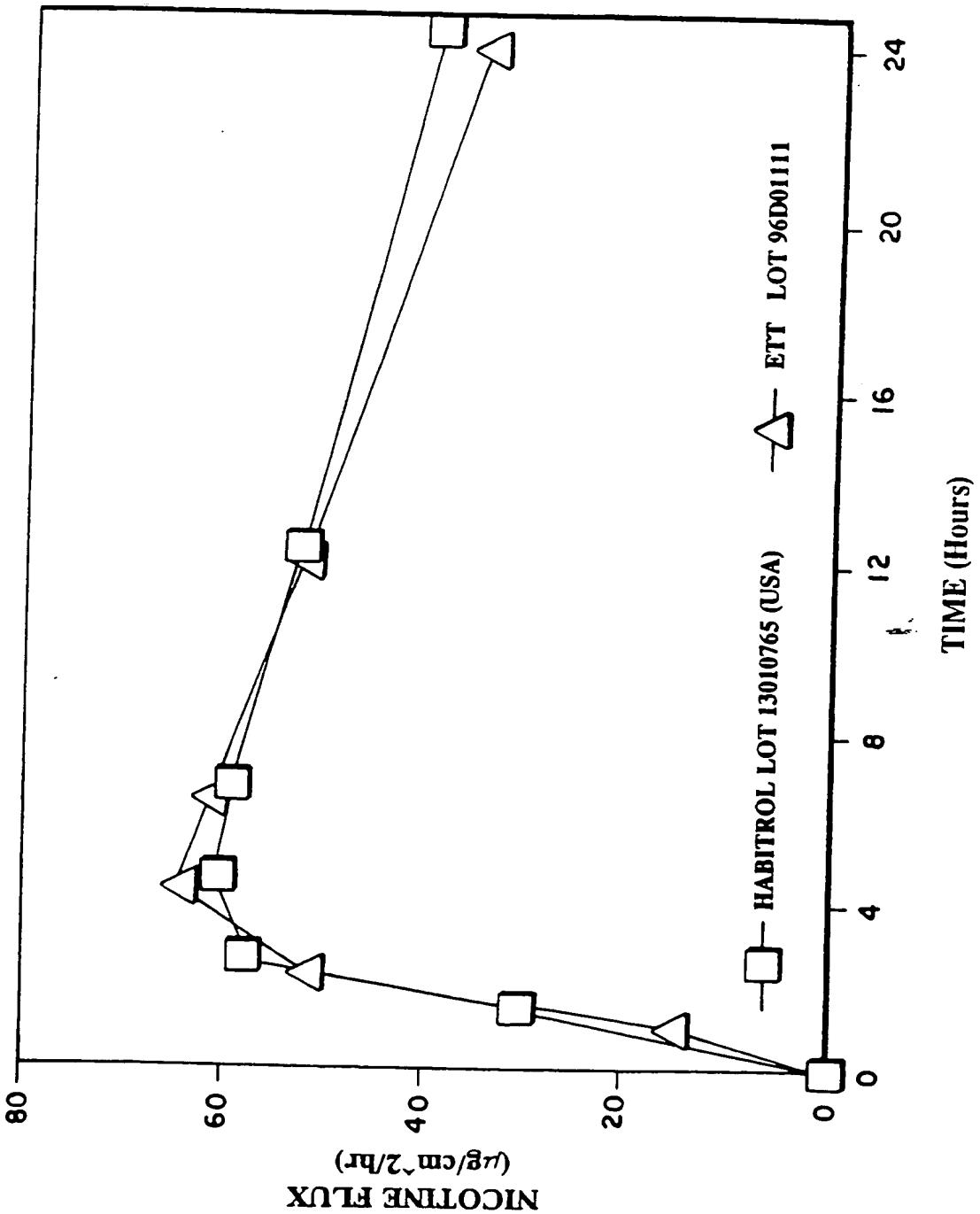
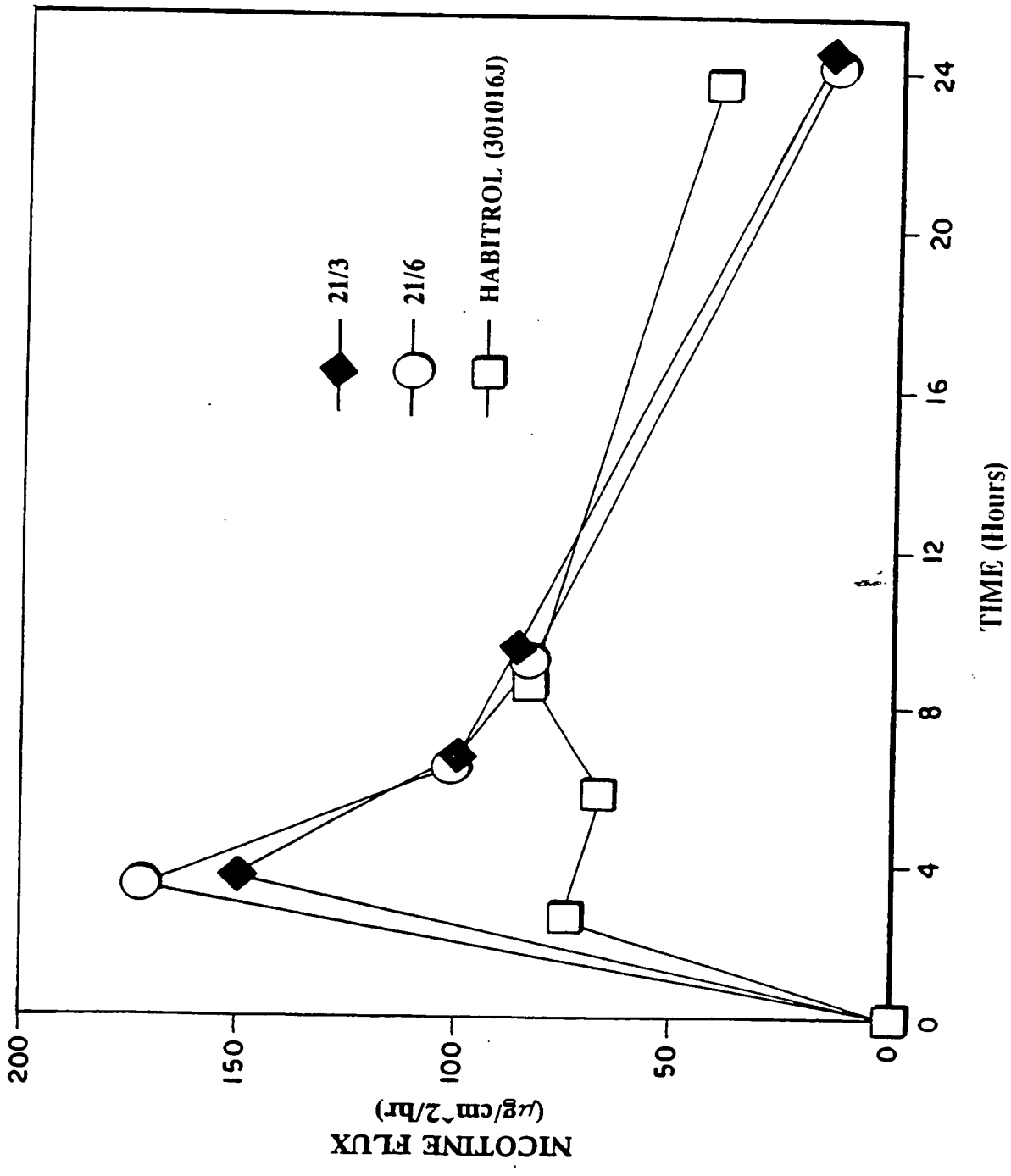


Fig. 3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0
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8
12
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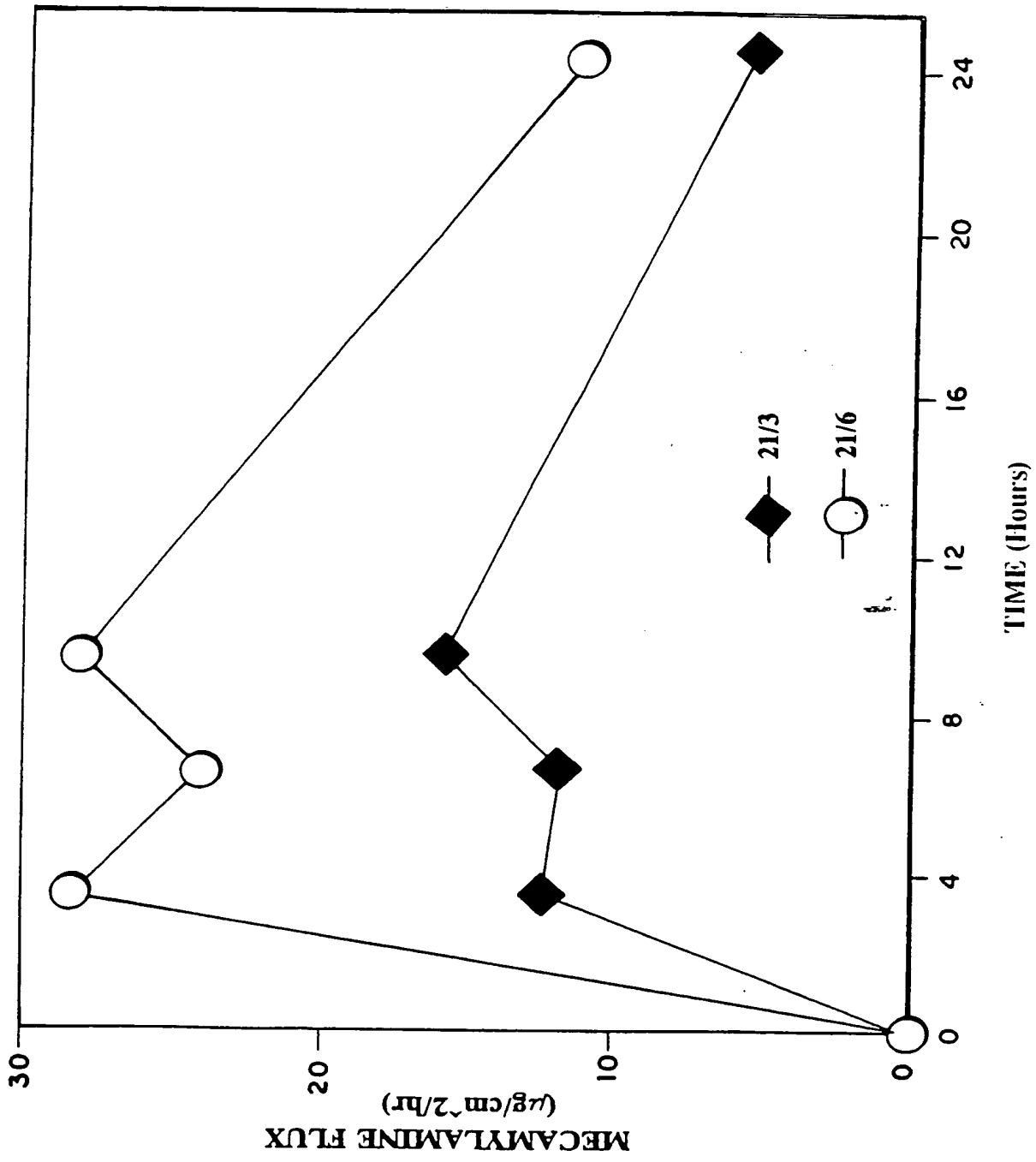
24
TIME (Hours)
21/3
21/6
HABITROL (301016J)

Fig. 4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(μg/cm^2/hr)
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TIME (Hours)
21/3
21/6

Fig. 5

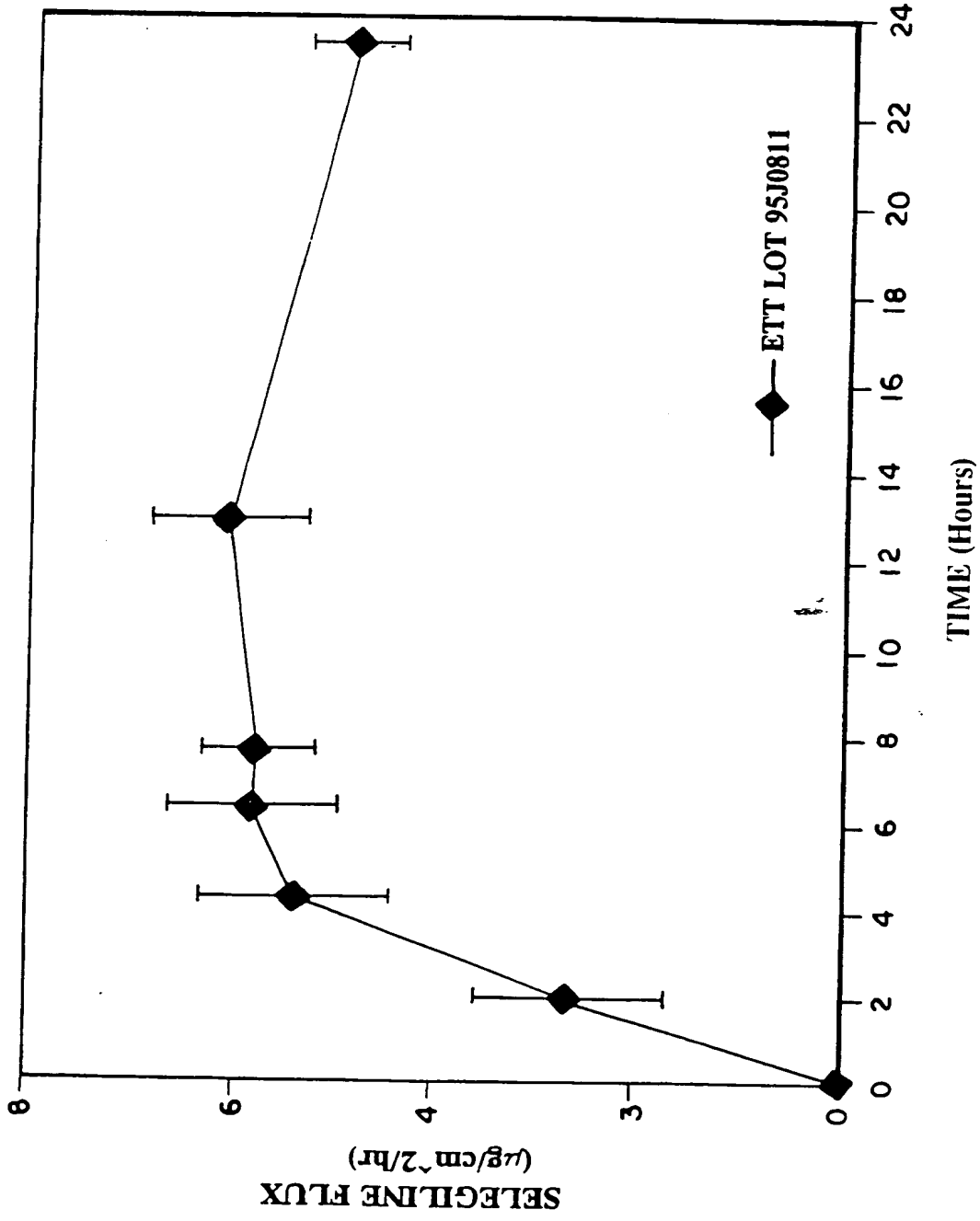
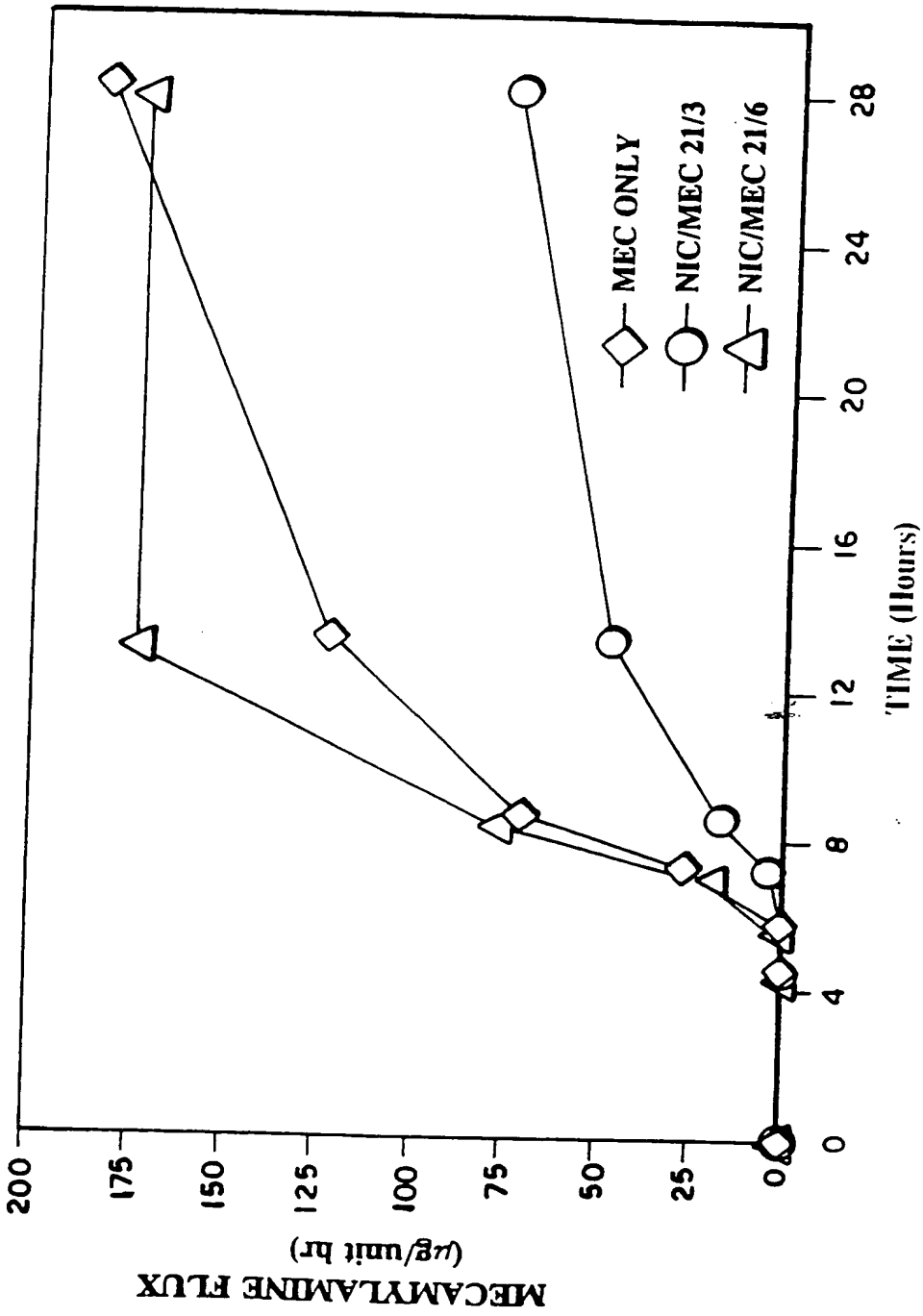


Fig. 6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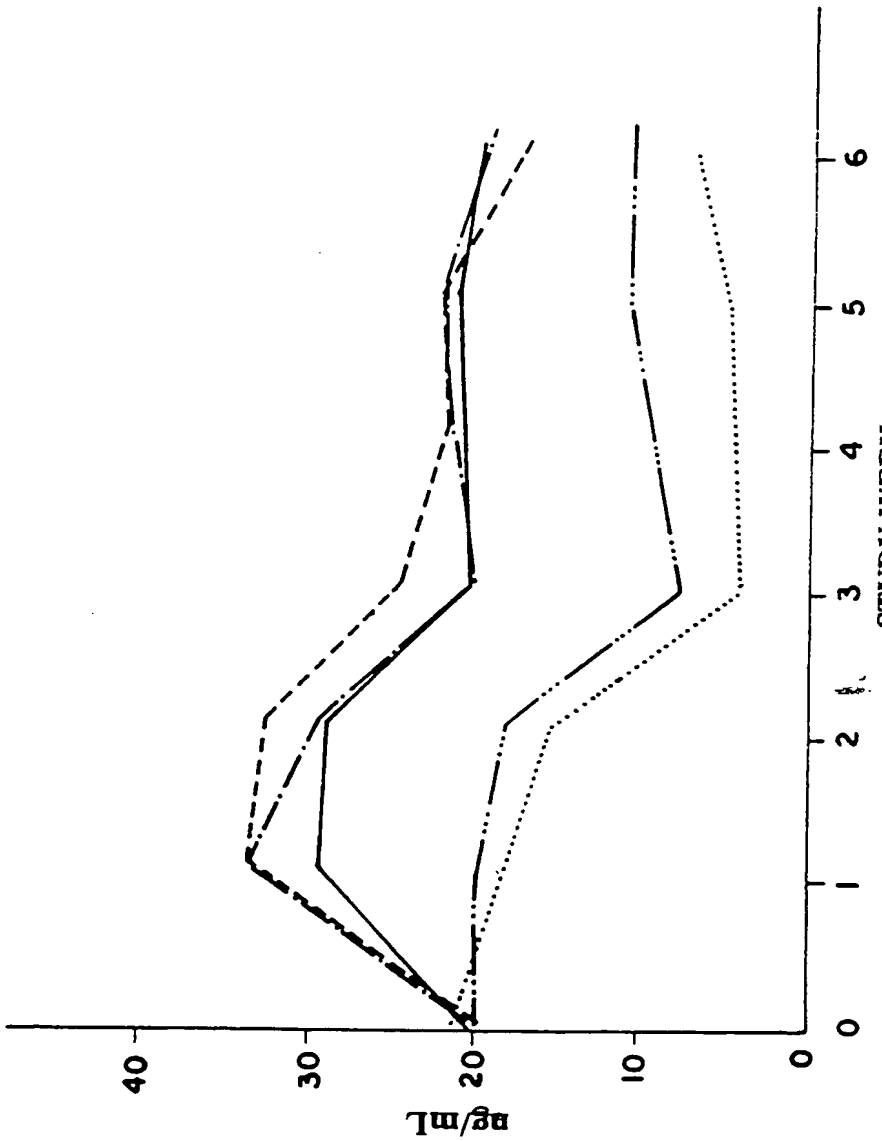
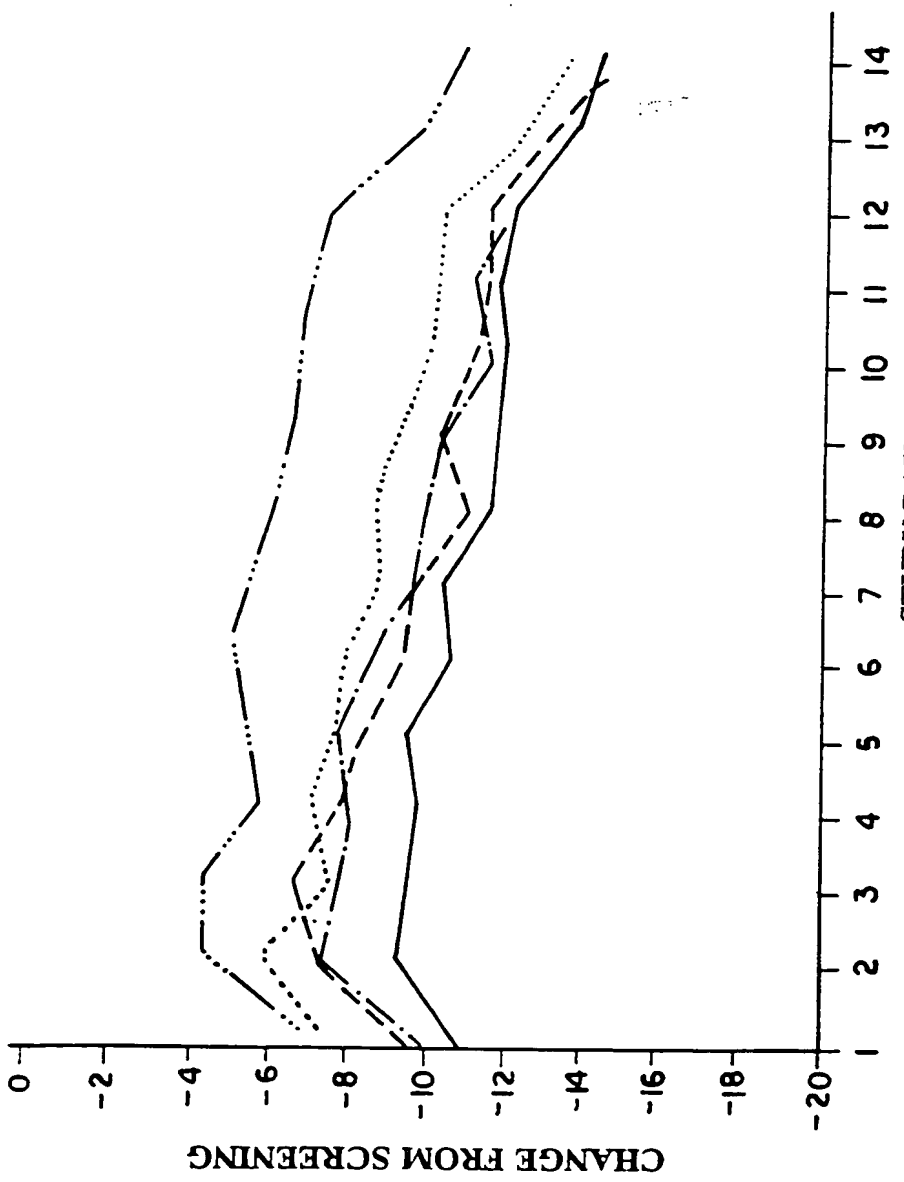
MEC ONLY
NIC/MEC 21/3
NIC/MEC 21/6

Fig. 7



Mean Nicotine Plasma Concentration by Treatment and Study Week

Fig. 8



Mean Observed Change in Number of Cigarettes by Treatment and Day

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/28697

A. CLASSIFICATION OF SUBJECT MATTER

A61K9/70,A61K31/465,A61K31/137,A61K31/131,C07D401/04,
C07C211/27,C07C211/36

According to International Patent Classification (IPC) or to both national classification and IPC 7

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K,C07D,C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/40085 A (NOVEN PHARMACEUTICALS, INC.) 19 December 1996, page 8, line 14 - page 9, page 18, line 32 - page 19, line 2, page 19, lines 18-37, examples 2-4, claims 1,3-6, 9,10,17,19-21,24.	1,2, 4,6-8, 10,11, 13
Y	--	3,5
X	WO 93/00058 A (NOVEN PHARMACEUTICALS, INC.) 07 January 1993, page 24, line 9, claims 1-5, 14-19,37-39,53-64,91-93.	1,2, 4,6
Y	--	3,5
Y	US 4717568 A (ECKENHOFF ET AL.)	3,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2000	27. 06. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	KRENN e.h.

INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/US 99/28697

C.(Conunuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	05 January 1988, abstract, column 18, lines 25,26. --	
X	US 5691365 A (CROOKS ET AL.) 25 November 1997, abstract, column 4, lines 20-29, column 14, lines 50-67, column 16, line 63. --	15-20
X	US 5316759 A (ROSE ET AL.) 31 May 1994, abstract, claims. --	21-26
A	US 5230898 A (HORSTMANN ET AL.) 27 July 1993, the whole document. --	1-26
A	US 5176915 A (HOFFMANN) 05 January 1993, the whole document. ----	1-26

ANHANG

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

To the International Search Report to the international Patent Application No.

ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/US 99/28697 SAE 268121

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La presénte annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l' Office.

Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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		EP B1 418248	29-12-1993
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Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

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